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HEMOCHROMATOSIS

REPORT OF A CASE WITH NECROPSY AND ANALYSIS OF THE LIVER

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In his monograph on hemochromatosis (1935) Sheldon [1] accepted from the literature 311 cases of the disease. The incidence of hemochromatosis found at necropsy has been reported by Rowen and Mallory [2] as 0.05 per cent in a series of 6,500 autopsies. Blanton and Healy [3] reported finding the condition at 0.08 per cent of 5,000 autopsies at Bellevue Hospital. The postmortem incidence reported from other sources ranged between 0.001 and 0.4 per cent. The diagnosis of the disease is made more often at autopsy than clinically, owing to the fact that pigmentation has been the factor which suggested the diagnosis. That cutaneous pigmentation is not an essential criterion for the diagnosis of hemochromatosis is well known. The four cardinal signs of the disease occur, according to Sheldon, in the following order: (1) enlargement of the liver (92 per cent), (2) pigmentation (84 per cent), (3) diabetes mellitus (78 per cent) and (4) genital hypoplasia, which is characterized by impotence and loss of secondary hair.

We shall report a case of hemochromatosis which was under observation from the time of onset of symptoms until death, eleven weeks later.

REPORT OF CASE

V. H., a 39 year old Irishman, entered the wards of the Third (New York University) Medical Division, Bellevue Hospital, on the night of Sept. 4, 1936, complaining of weakness and loss of 16 pounds (7.3 Kg.) during the preceding two weeks and vomiting for the preceding three days. During this period there had been a marked loss of appetite, and the diet had been totally inadequate. The patient was a paint mixer and for twelve years had been exposed to zinc, lead and arsenic. He had had malaria in 1915; there was a history of alcoholism, and

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1. Sheldon, J. H.: Hemochromatosis, London, Oxford University Press, 1935.
2. Rowen, H. S., and Mallory, F. B.: Am. J. Path. **1**:677, 1925.
3. Blanton, W. B., and Healy, W.: Hemochromatosis, Arch. Int. Med. **27**: 406 (April) 1921.

he had been admitted to another hospital in 1929, after a four day attack of abdominal cramps, vomiting and diarrhea.

On admission, physical examination showed that the patient was normally developed and rather poorly nourished, and appeared chronically ill (fig. 1). The temperature was 99 F. There was no respiratory distress. A marked odor of acetone on the breath was noted. There was a dusky appearance of the skin of the face, hands and legs. The head was normal, save for telangiectasis over both cheeks. Examination of the eyes showed the pupils, conjunctivas and scleras

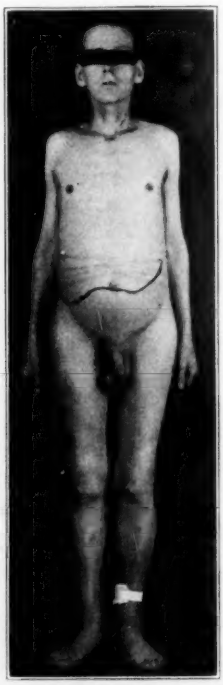

Fig. 1.—Appearance of the patient on Oct. 29, 1936, showing absence of secondary hair, protrusion of abdomen (ascites) and edema of the abdominal wall. The lower border of the liver is outlined.

to be normal. Examination of the ears, nose and throat showed the teeth and gums to be in poor condition. There was no lead line. The tongue was dry. The neck was normal, with no masses. The thyroid gland was not palpable. The lungs were clear throughout. The point of maximum intensity of the heart beat was diffuse in the fifth intercostal space, inside the midclavicular line. The sounds were of good quality. The aortic and the pulmonic second sound were equal. There were no thrills, gallop or rub. The rhythm was of the regular sinus type. The pulse rate was 90. The blood pressure was 125 systolic and 90 diastolic. There was a sense of fulness in the epigastrium. The edge of the

liver was felt 4 fingerbreadths below the costal margin and extended diagonally to the left upper quadrant. The edge was firm, sharp, irregular and nontender. The spleen was not felt. There was no fluid wave or shifting dulness. There were no superficial dilated veins. Cyanosis was present over the upper and lower extremities. There was no edema or clubbing. Neurologic examination showed no abnormality. There was complete absence of secondary hair, save for a sparse beard.

Urinalysis on admission showed a volume of 600 cc., 39 Gm. of sugar and 4 plus reactions for acetone and diacetic acid. The sugar content of the blood was 570 mg. per hundred cubic centimeters and the carbon dioxide–combining power was 25 volumes per cent. The diagnosis on admission was: (1) diabetes mellitus with ketosis and (2) cirrhosis of the liver.

Treatment for diabetic ketosis was begun. After a gastric lavage with a solution of sodium bicarbonate, an infusion of 5 per cent dextrose in physiologic solution of sodium chloride was started and insulin given. The patient's condition remained good, and six hours after admission urinalysis showed a small amount of sugar and a faint reaction for acetone. During this period the patient received 3,500 cc. of physiologic solution of sodium chloride, 185 units of insulin and 175 Gm. of dextrose. For the remainder of the night the patient was fed orange juice, and small doses of insulin were given. Sixteen hours after admission the carbon dioxide–combining power of the blood was 55 volumes per cent.

Other laboratory data on admission were: 4,670,000 red blood cells; 100 per cent, or 14.5 Gm., of hemoglobin; and 6,900 white blood cells, with a normal differential count and smear. The Wassermann reaction was negative; urinalysis showed no abnormality save for the presence of sugar and ketone bodies.

The morning after admission the patient was in good condition and was given a diet of 250 Gm. of carbohydrate, 80 Gm. of protein and 85 Gm. of fat in six feedings, with 15, 10, 10, 10, 10 and 10 units of insulin, respectively, at each feeding. It was observed that the dusky appearance noted the night before was due to a bluish gray "slate" color, which was most marked over the face and extremities but was also present over the rest of the body. The diagnosis of hemochromatosis was suggested.

COURSE IN THE HOSPITAL

First Period.—The patient was soon able to eat three regular meals a day. An additional feeding of orange juice and insulin was given at midnight. He remained in good condition for about four weeks. During this period various diagnostic procedures were performed. Roentgen examination of the heart and lungs and the stomach and intestines, gastric analysis and proctoscopic examination showed no abnormality. Electrocardiograms taken early in the course and later showed no change. There was no deviation of the electrical axis; the PR interval and QRS complex were of normal duration; QRS waves were slurred in leads I and II; the T wave was diphasic in lead II and inverted in lead III. The rhythm was of the regular sinus type, with auricular premature contractions. Communication with the hospital to which the patient was admitted in 1929 verified his occupational history. The report stated that there was "a peculiar cyanosis of his entire body. The liver was enlarged and the spleen palpable."

A bromsulphalein excretion test one week after admission (September 11) showed 5 per cent retention of the dye at the end of one-half hour. A biopsy specimen of skin taken during this period showed "a moderate deposition of pigment which stained brown with hematoxylin and eosin and blue with the prussian blue stain. The diagnosis was hemochromatosis."

During this period of well-being the patient was on a diet of 275 Gm. of carbohydrate, 80 Gm. of protein and 85 Gm. of fat. His insulin requirement fell from 115 units a day early in September to 60 or 75 units a day the next month (fig. 2). Slight glycosuria was permitted. There were no hypoglycemic reactions.

Second Period.—During October, after the patient had been in the hospital for five weeks, ascites and edema of the lower extremities first made their appearance (October 12). At this time the albumin-globulin ratio was 3:2.5. A bromsulphalein test (October 28) showed 100 per cent retention of the dye after one-half hour. Proctoscopic examination again revealed a normal mucous membrane. Ascites progressively increased, but was never distressing. The patient lost 7 pounds (3.2 Kg.) after one intravenous injection of 2 cc. of mercupurin (a mercurin-theophylline preparation). The second period of four weeks (after the appearance of the ascites) was characterized by minor complaints, notably epigas-

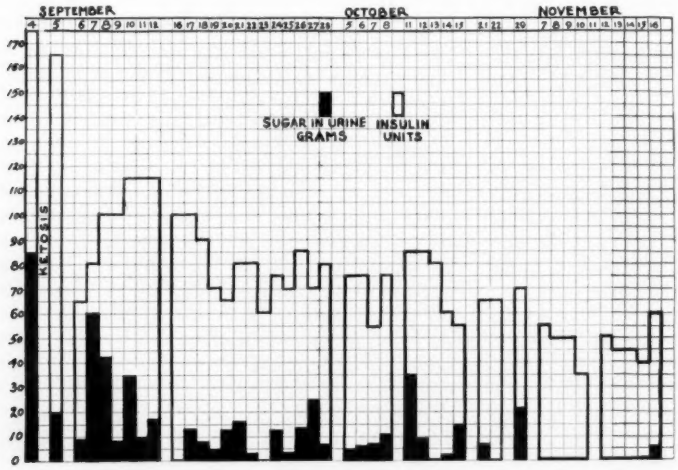

Fig. 2.—Chart showing the insulin requirement and degree of glycosuria during hospitalization.

tric distress and nausea, but these were never more than mild. The same diet was continued, and approximately the same doses of insulin. There was no apparent change in the cutaneous pigmentation. On October 22 a drop in the red blood cells, to 3,800,000, with 90 per cent, or 12.6 Gm., of hemoglobin, was noted. The only qualitative change in the blood smear was the presence of a few round macrocytes. The white blood cell count was normal. The van den Bergh reaction was negative, and the icterus index was not elevated. No methemoglobin was found in the blood. An analysis of the urine showed the presence of 0.05 mg. of lead in 1,300 cc. The examination of the urinary sediment showed the presence of intracellular iron-containing pigment. The diet during this period had been augmented by 1 drachm (3.88 Gm.) of Vegex three times a day and 1 fluidrachm (3.7 cc.) of iron and ammonium citrates (50 per cent solution) three times a day.

Terminal Period.—The last week of the patient's illness was ushered in by a severe attack of diarrhea, which lasted but one day. There was no evidence of

ketosis, and the patient was apparently well the next day. Three days later it was noted that the veins in the neck were distended, but did not pulsate or fill from below. There was edema of the anterior wall of the chest. A gallop rhythm was heard over the precordium. There was no clinical evidence of enlargement of the heart. Electrocardiograms taken at this time showed no change from the preceding ones. Determinations of the sugar content of the blood on three days during the last week showed 250 mg. per hundred cubic centimeters, at 2 p. m.; 216 mg., at 2 p. m., and 180 mg., at 4:30 p. m. The carbon dioxide-combining power on the day before death was 47.5 volumes per cent.

On the day before death edema spread over the entire body to include the face. Vomiting, dyspnea and cyanosis were moderate. Mild ketosis was treated successfully with intravenous injections of dextrose and small doses of insulin. Abdominal paracentesis was performed, without relief. The terminal episode was one of pulmonary and cerebral edema, with the development of left hemiplegia. Intravenous injection of hypertonic solutions produced no relief. Examination of the throat revealed no evidence of edema of the larynx. The insulin requirement during this period is shown in the chart (fig. 2). The downward course was rapid, with marked pulmonary edema. The patient died on November 18, eleven weeks after admission. The final diagnosis was hemochromatosis and diabetes mellitus.

NECROPSY REPORT

Macroscopic Examination.—The external features given were confirmed at the postmortem table. When the abdomen was opened about 3 liters of clear sanguineous fluid was found in the peritoneal cavity. The edge of the liver extended 8 cm. below the right costal margin and 12 cm. below the xiphoid process. It completely covered the spleen in the left upper quadrant. Each pleural cavity contained about 1 liter of serosanguineous fluid. There was marked congestion of both lungs and the trachea and bronchi. The heart weighed 400 Gm. There was moderate dilatation of all chambers, particularly the right ventricle. The superior and the inferior vena cava were normal. There were no gross abnormalities. The arterial system was thin walled and natural throughout. The aorta was normal save for scattered yellowish plaques in the abdominal portion, measuring 3 or 4 mm. The liver weighed 3,500 Gm. Its capsular surface was purplish brown and glistening, but slightly nodular, the individual nodules measuring 2 or 3 mm. in diameter. The liver cut with slightly increased resistance, presenting a bright brown surface which was diffusely nodular. The original hepatic nodules could not be recognized. The spleen weighed 450 Gm. The pulp was deep red, and numerous follicles could be seen in its substance. The pancreas was altered considerably in appearance. The color was deep chestnut brown and the substance firm. In some areas the lobulations could not be made out. The stomach presented a deep brown surface, with many submucosal pinhead-sized areas of hemorrhage. Similar changes were observed in the duodenum and the first 3 feet (90 cm.) of the jejunum. Scattered areas of submucosal hemorrhage were seen throughout the remainder of the gastrointestinal tract. The kidneys showed multiple infarcts and fetal lobulations. The adrenal glands appeared normal in size. The medulla appeared cystic, and the cortex was discolored a greenish brown. The thyroid gland, testes and bladder appeared normal. A brownish coloration was noted in the left lobe of the prostate. The lymph nodes along the abdominal aorta and about the pancreas were a deep chestnut brown and of normal size. The brain showed no abnormalities grossly.

Microscopic Examination.—Liver: There was considerable distortion of the hepatic pattern. Thick, dense layers of fibrous tissue surrounded the portal zones, breaking the hepatic tissue into small nodules. Many of the hepatic cells were well preserved, but there were many areas of atrophy, particularly in the central portions of the lobules. Large amounts of brown-yellow iron-containing pigment were present, with numerous macrophages within the fibrous stroma. This pigment in less coarse form was seen within the polygonal and Kupffer cells. A few bile ducts contained pigment. The diagnosis was hemochromatosis and portal cirrhosis (pigment).

Lungs: Several brown-pigmented iron-containing macrophages were seen within the alveoli. A few small bronchioles contained uniform iron pigmentation, and many small irregular deposits of hemosiderin were present within the walls of the arteries. The diagnosis was slight hemochromatosis and patchy atelectasis.

Pancreas: The lobular structure was preserved, but changes were present within the individual lobules. A somewhat increased stroma was seen along the course of the acini, which varied in density, in some portions merely separating and elsewhere breaking up and replacing the cells. Embedded in the stroma were many large and small macrophages in which there was much iron-containing pigment in coarse granules. The acinar cells also contained pigment, but in lesser amounts. The islets of Langerhans appeared decidedly less numerous than normal. They were generally free from pigmentary and other changes. The arterioles showed slight hyaline thickening. The diagnosis was hemochromatosis with slight intralobular pigmentary cirrhosis and arteriosclerosis.

Thyroid: Most of the follicles were large and filled with colloid. There was considerable yellow-brown iron-containing pigment within the follicular epithelioid cells and to a much less extent in the capillary walls. Small particles were infrequent within the stroma, although most of the latter was free from pigment.

Spleen: Yellow-brown iron-containing pigment was seen in many macrophages within the lymphoid deposits and pulp, in the trabecular elements and arterial walls and to a lesser extent within the pulp stroma. The diagnosis was hemochromatosis and chronic passive congestion.

Myocardium: The fibers appeared increased in width, and there were diffuse deposits of particles of coarse brown iron-containing pigment within the bundles. Pigment was present within many macrophages between the fibers. There was slight focal intrafascicular fibrosis. The aorta was normal. The diagnosis was hemochromatosis and focal intrafascicular fibrosis.

Kidneys: In the noninfarcted areas the structure was normal. Iron stains showed deposition of pigment within the cells of the tubules, particularly the loops of Henle, and there was a slight amount in the glomerular tufts. The diagnosis was slight hemochromatosis and multiple infarctions with beginning organization.

Stomach: The mucosal and glandular cells were heavily laden with iron-containing pigment. The plical epithelial cells of the jejunum were only slightly stained.

Adrenal Glands: The structure was normal. There was considerable deposition of iron-containing pigment, particularly in the outer layer of the cortex. The diagnosis was hemochromatosis.

Prostate: Iron-containing pigment was present in the lining cells of many follicles and in the interstitial tissue. The diagnosis was hemochromatosis.

Testes: The basement membrane was thickened. Many groups of tubules were fibrotic, and those which were still cellular failed to show evidence of complete

spermatogenesis. In a few small blood vessels there was iron-containing pigment within the endothelial cells.

Brain: Section through the pons showed an area of necrosis on each side of the base, involving some of the fibers of the pyramidal tract. These softened areas contained no phagocytes. In places there were small perivascular hemorrhages, and in the fourth ventricle there was slight ependymitis such "as is seen sometimes in syphilis or alcoholism." The nature of these necrotic foci was not clear, but they were "probably due to occlusion of the small arteries." The diagnosis was bilateral areas of softening in the pons.

COMMENT

Urine.—(*A*) Hemosiderin: Intracellular granules of hemosiderin were found in the urine in this case by the technic described by Rous.[4] According to Sheldon,[1] use of this technic was mentioned in 10 reported cases and gave positive results in 8. When one considers the severity of tubular siderosis which may be found in this disease, it is not surprising that cast-off hemosiderin-bearing cells are present in the urinary sediment. While a positive reaction to the test is not limited to this disease, the simplicity of a search for these granules suggests itself as a valuable adjunct in the verification of the diagnosis.

(*B*) Melanin: Uhlenbruck[5] described a case in which melanin was present in the urine. No melanin was found in the urine in our case, although tests were made by the method of Haden and Orr.[6] The cutaneous pigmentation in this disease has been ascribed to both melanin and hemosiderin by several authors. Hellier[7] has shown the presence of these pigments in the skin in this disease. In our case a biopsy specimen of skin of the lower part of the leg failed to reveal any increase in melanin, while hemosiderin was seen in abundance. If the pigmentation were due to an increase in the production of melanin such as one finds in melanotic tumors, this might manifest itself by the presence of urinary melanin. However, the absence of melanin in greater quantity than that found in normal skin, the slaty color of the skin and the absence of melanin in the urine all militated against an abnormality of melanin production as a factor in the case.

(*C*) Porphyrins: During the terminal period of the patient's illness the urine was examined for porphyrins by the method of Brugsch,[8] with negative results. Coproporphyrin I or III was not demonstrated by the method of Dobriner.[9] This is interpreted as additional evidence of acute hepatic insufficiency.

4. Rous, P.: J. Exper. Med. **28**:645, 1918.
5. Uhlenbruck, P.: Deutsches Arch. f. klin. Med. **167**:80, 1930.
6. Haden, R. L., and Orr, T. G.: Bull. Johns Hopkins Hosp. **35**:58, 1924.
7. Hellier, F. F.: Brit. J. Dermat. **47**:1, 1935.
8. Brugsch, J. T.: München. med. Wchnschr. **81**:1546, 1934.
9. Dobriner, K.: J. Biol. Chem. **113**:1, 1936.

Ascitic Fluid.—The ascitic fluid revealed no hemosiderin in the cellular sediment obtained by centrifuging 200 cc. and examined by the method used for urinary sediment, nor was there any melanin in this fluid when tested by the method of Haden and Orr.[6]

Pigments Present in Hemosiderosis.—In 1889 von Recklinghausen[10] described two pigments which were present in hemochromatosis: (*a*) an iron-containing pigment, described previously by Neumann as hemosiderin, and (*b*) a noniron-containing pigment, hemofuscin. The first, hemosiderin, occurs in the secreting cells of the glands, the connective tissue of these glands, the lymph nodes, striated muscle, the cartilages and synovia and the walls of the blood vessels. This pigment occurs in fine single granules or granules clumped together in masses, varying from deep yellow to brown. The granules are angular, with a sharp outline. The pigment is insoluble in alkalis and soluble in acids.[11] Aniline dyes or alum hematoxylin does not stain the pigment,[12] but potassium ferrocyanide in acid medium stains the granules a blue green, which on heating becomes the prussian blue of the ferric ferrocyanide reaction. Potassium ferricyanide and potassium thiocyanate give no reaction.[11] There are points of dispute concerning the exact nature of the pigment, but the fundamental constitution is well established. Many observations have shown the presence of iron, and Sheldon credited Auscher and Lapicque (1895-1898) with being the first to call the pigment a hydrated oxide of iron existing in combination with organic matter. This finding has been substantiated by Cook[11] and by Asher,[13] both working with horse spleen. Jacoby,[14] in a study of the liver of a patient with hemochromatosis, concluded that the iron was combined with protein.

While we carried out no detailed investigation, we attempted to elicit several reactions to show the nature of the pigment, and we were led to believe that the iron present existed in the ferric state and that it occurred with a non-iron moiety. Cook found that the hemosiderin consisted of an iron compound which could be removed from the granules by treatment with acid, leaving the substrate practically intact. This we, too, observed. Acid extracts yielded reactions similar to those described by Cook for potassium ferrocyanide, potassium thiocyanate and sodium hydroxide. However, our observations differed as to the behavior of tissue on direct application of ferrocyanide and ferricyanide in the presence of acid. We obtained a positive reaction for ferric iron

10. von Recklinghausen: Berl. klin. Wchnschr. **26**:925, 1889.
11. Cook, S. F.: J. Biol. Chem. **82**:595, 1929.
12. Mallory, F. B.; Parker, F., and Nye, R. N.: J. M. Research **42**:461, 1920.
13. Asher, T.: Ztschr. f. physiol. Chem. **220**:97, 1933.
14. Jacoby, M.: Biochem. Ztschr. **230**:225, 1931.

when ferrocyanide was applied, while Cook reported that the tissue required warming; in our experiments the tissue yielded Turnbull's blue with ferricyanide for ferrous iron, which was much fainter, however, than the reaction for ferric iron and may have been due to the fact that the examination was carried out several days post mortem, allowing for change of the original ferric iron.

Iron and Copper in the Liver and Spleen.—The increase of iron and copper in the various tissues in hemochromatosis has been amply confirmed. We analyzed the liver and spleen in our case by the method of Kennedy,[15] using a photoelectric colorimeter instead of the colorimeter specified by the author. The copper content was determined by the method of McFarlane,[16] except that the iron was removed by precipitation as the hydroxide.

Our results are listed in table 1, together with those of other authors for persons with similar diseases and for normal subjects. Ramage and

TABLE 1.—*Iron and Copper Contents of the Liver and Spleen of Patients with Hemochromatosis and of Normal Subjects*

	Liver		Spleen	
	Iron, Gm. per 100 Gm. (Dry)	Copper, Mg. per 100 Gm. (Dry)	Iron, Gm. per 100 Gm. (Dry)	Copper, Mg. per 100 Gm. (Dry)
Our patient	2.33	6.5	0.56	8.3
Other patients	3.6 to 2.1	4 to 40	0.27 to 0.13	10.4
Normal subjects of various authors	0.05	2.5	0.14	2.7

Sheldon [17] determined the iron content of the liver and spleen by the method used by us; our method of copper determination differed from theirs.

From the composite data (table 1) the increase in iron and copper in the liver and spleen in this case is apparent.

Vitamin A.—In 1935 Ralli and her associates [18] reported the vitamin A content of the liver in a case of hemochromatosis, with the findings in 7 cases of diabetes mellitus and in 13 cases in which diabetes was not present. The method of Carr and Price [19] was used in these determinations, in which the concentration of the vitamin is expressed in the blue units of the Lovibond tintometer. In the present case

15. Kennedy, R. P.: J. Biol. Chem. **74**:385, 1927.
16. McFarlane, W. D.: Biochem. J. **26**:1022, 1932.
17. Ramage, H., and Sheldon, J. H.; Quart J. Med. **4**:121, 1935.
18. Ralli, E. P.; Brandaleone, H., and Mandelbaum, T.: J. Lab. & Clin. Med. **20**:1266, 1935.
19. Carr, F. H., and Price, E. A.: Biochem. J. **20**:497, 1926.

vitamin A was determined by the method of Davies,[20] with the Hilger vitameter; the results are expressed in U. S. P. XI units. The value previously reported by Ralli for a patient with hemochromatosis was 1,905 blue units per hundred grams of liver, while the lowest found among patients with diabetes was 9,680 blue units and the corresponding figure for normal subjects was 8,800 blue units. The lowest value for a diabetic and a normal subject were thus five and four and one-half times as great as that of the patient with hemochromatosis. In a series of cases of chronic disease Wolff [21] reported the average value to be 20,600 blue units per hundred grams, while in a series of 25 cases of diabetes the average was 48,400 blue units per hundred grams. In a series of 6 cases of cirrhosis of the liver the average was 7,100 blue units per hundred grams, and the corresponding value in 3 cases of acute yellow atrophy was 14,700 blue units. The low value for the vitamin in cases of cirrhosis as contrasted to that in atrophy was

TABLE 2.—*Lipids in the Liver of a Patient with Hemochromatosis*

	Percentage	Percentage of Total Lipids
Total lipids	4.97	..
Unsaponifiable material	0.89	..
Total fatty acids	3.40	..
Iodine number-fatty acids	95.0	..
Lipid phosphorus	0.08	..
Phospholipid	2.09	42
Cholesterol (free + total)	0.334	..
Neutral fat	2.12	43

confirmed by Breusch and Scalabrino.[22] In our case the vitamin A content of the liver was 53 U. S. P. XI units per gram of wet tissue. This value is the lowest found to date in a series under investigation at present in this laboratory.[23]

We do not intend to draw any conclusion from these data, but it appears from the few figures available that the vitamin A content of the liver in hemochromatosis is far below that in nondiabetic chronic disease, diabetes, acute atrophies and cirrhosis of the liver.

Lipids in the Liver.—The various lipids in the liver were determined by the methods reported by Rubin, Present and Ralli,[24] of this laboratory. The results are given in table 2. The total lipid content of the liver (4.97 Gm. per hundred grams of liver) in our case is between the values reported by Theis [25] (3.45 to 3.04 per cent) and those by Breusch

20. Davies, A. W.: Biochem. J. **27**:1770, 1933.
21. Wolff, L. K.: Lancet **2**:617, 1932.
22. Breusch, F., and Scalabrino, R.: Ztschr. f. ges. exper. Med. **94**:569, 1934.
23. Flaum, G., and Stueck, G. H. Jr.: Unpublished data.
24. Rubin, S. H.; Present, C., and Ralli, E. P.: J. Biol. Chem. **121**:19, 1937.
25. Theis, E. R.: J. Biol. Chem. **82**:327. 1929.

and Scalabrino [22] (5.16 to 6.43 Gm. per hundred grams). The phospholipid–neutral fat ratio of approximately 1 is lower than that (1.5) reported by Theis. The value for lipid phosphorus (0.08 Gm. per hundred grams of liver) is in the range reported by Breusch and Scalabrino (0.098 to 0.066 Gm. per hundred grams). The values just reported are included in a study of the lipid content of normal and abnormal human livers being made in this laboratory at present.

General Comment.—The case described illustrates the four classic clinical features of the disease; namely, enlargement of the liver, cutaneous pigmentation, diabetes mellitus and loss of secondary hair. It is well known that patients may survive the pigmentation and enlargement of the liver for many years, but that with the onset of diabetes the prognosis is limited. In this instance we have evidence of the presence of pigmentation and enlargement of the liver at least seven years prior to the final admission. During this period there were no symptoms save one gastrointestinal upset (possibly unrelated) in 1929. If we assume that the onset of diabetes occurred at the time of symptoms of that disease, the patient survived this by only three months.

"Resistance" to insulin has been reported in cases of hemochromatosis.[26] A tendency to hypoglycemia has also been reported.[27] Our patient demonstrated a good response to insulin therapy on a high carbohydrate diet, both while he had ketosis and while he was ambulatory, as evidenced by a progressively lower insulin requirement while he was on a diet of constant composition.

Reports of liver function tests in cases of hemochromatosis are few in the literature. In our case there was a normal result in the bromsulphalein excretion test (5 per cent retention) early in the patient's period of hospitalization. Seven weeks later there was 100 per cent retention of the dye. The rapidly progressing hepatic dysfunction, together with the onset of diabetes, the appearance of ascites and a mode of death similar to the "liver failure" seen in the terminal stage of cirrhosis of the liver, constituted the terminal episode of a long-standing disease. It has been suggested by some observers [28] that ascites is more common in hemochromatosis after insulin therapy. A more likely conception is that the diabetes is the forerunner of ascites in rapidly progressing dysfunction of the liver.

That there is no "characteristic electrocardiogram" is not difficult to understand. The extent and location of the pigmentation and fibrosis

26. Miller, H. A., and Heimark, J. J.: Minnesota Med. **14**:260, 1931. Root, H. F.: New England J. Med. **201**:201, 1929.

27. Stetson, R. P., and Peters, J. P.: Carbohydrate Metabolism in a Case of Hemochromatosis, Arch. Int. Med. **50**:226 (Aug.) 1932.

28. Bingel, A.: München. med. Wchnschr. **79**:1750, 1932.

of the myocardium would determine any change in the electrocardiogram, particularly if the process involved any of the ramifications of the conduction system. Pigmentation alone may not alter the electrocardiogram.

Sheldon has pointed to the possible correlation of the clinical findings of loss of hair and impotence with the postmortem observations in the endocrine glands. Changes are more striking in the anterior lobe of the pituitary gland and the cortex of the adrenals, both of which structures are known to be associated with the clinical features mentioned. In our case a history of impotence was not obtained, but the absence of secondary hair has been pointed out. There was marked pigmentation of the outer layer of the adrenal cortex; unfortunately, the pituitary gland was not saved for microscopic section.

Various toxic agents have been suggested as the etiologic factor in this disease. In 1921 Mallory, Parker and Nye [12] offered chronic copper poisoning as a likely one. This view was also expressed by Hall and Butt,[29] but was denied by Flinn and Von Glahn [30] and by Polson.[31] Alcohol, acting alone or with copper as a contaminant, has been suggested as another possible agent. In our case there was a history of alcoholism over a period of years and of occupational exposure to zinc, lead and arsenic during twelve years the patient spent as a paint mixer. Lead was found in the liver in a concentration of 0.12 mg. per 500 Gm. Arsenic was absent; the copper and the iron content have been reported.

SUMMARY

We have described a case of hemochromatosis in a 39 year old white man with enlargement of the liver, cutaneous pigmentation, diabetes mellitus and absence of secondary hair. The course of the disease over eleven weeks is presented, including diabetic ketosis on admission, the initial appearance of ascites and a mode of death typical of the "liver failure" seen in cirrhosis of the liver. The postmortem observations are recorded, together with an analysis of the liver for lipids, heavy metals and certain pigment reactions.

Dr. Douglas Symmers, director of the pathologic laboratories, Bellevue Hospital, permitted us to use the protocol of the necropsy summarized in this report.

29. Hall, E. M., and Butt, E. M.: Experimental Pigment Cirrhosis Due to Copper Poisoning: Its Relation to Hemochromatosis, Arch. Path. **6**:1 (July) 1928.
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RATE OF REMOVAL OF THORIUM DIOXIDE FROM THE BLOOD STREAM

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AND
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In order to obtain data concerning the function of the cells which clear the blood of large particles, the velocity of removal from this fluid of colloidal thorium after intravenous injection was determined under normal conditions for dogs subsequently subjected to procedures designed to alter the activity of these cells.

There have been several previous studies of reticuloendothelial activity, determining the rate of removal of injected large molecular masses in the form of bacteria,[1] colloidal metals (silver,[2] manganese [3] and saccharated ferric oxide [4]), quartz,[5] carbon,[2a] egg yolk,[6] egg albumin,[7] bilirubin [8] and various dyes (congo red,[9] brilliant vital red,[10] trypan blue,[11] bromsulphalein [12] and a series of acid and basic dyes [13]). Difficulties follow the use of all these substances which do not attend the use of thorium. All the dye studies have been complicated by excretion from the organism during the test period, so that the rate of removal from the blood represented in part ingestion by macrophages and in part elimination from the body. The injected neutral fat has been in the

From the Department of Surgery, the University of Chicago.

Aided by a grant from the Douglas Smith Foundation for Medical Research.

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form of egg yolk, to which the animals have become allergic, limiting the number of observations. The methods of identification have been unsatisfactory for the determination of quartz and carbon. Difficulties have been experienced with the colloidal metals either in the preparation of a satisfactory suspension, as in the case of manganese dioxide, or through toxicity, in the case of silver and iron, limiting the amount that can be injected. The bacterial removal was determined by colony counts.

Colloidal thorium dioxide seemed to be more satisfactory than any substance previously used. It consists of large electronegative molecules, submicroscopic in size and insoluble in aqueous solutions, which are stored in the cells of the so-called reticuloendothelial system. It is eliminated in the merest traces from the organism.[14] Further, large amounts can be injected intravenously without immediate toxic effect, and satisfactory methods exist for the chemical estimation of thorium. An objection to its use lies in its radioactivity, toxic changes being produced after many months, but no immediate toxic effects were detected from the doses used.

METHOD

Colloidal thorium dioxide[15] was injected intravenously in doses of 9 to 12 cc. (2.25 to 3 Gm. of thorium dioxide) into 19 normal dogs, weighing 8 to 20 Kg. Each dog was always given the same amount of thorium; the maximum amount was 38.5 Gm. of thorium dioxide over three months. After the injection 7 cc. of blood was withdrawn at frequent intervals for three hours in a syringe moistened with saturated potassium oxalate and was centrifuged immediately for ten minutes at high speed in a tube to which 1 drop of this anticoagulant had been added. The amount of thorium was determined by a micromethod, and a curve was constructed with respect to the time interval.

The chemical method of estimating the amount of thorium was a slight modification of a standard method.[16] All analyses were made in triplicate. One or two cubic centimeters of plasma was digested with 2 cc. of concentrated sulfuric acid and fuming nitric acid over a microburner until the carbon had been destroyed. After the solution had been cooled in an ice bath, about 40 Gm. of pulverized ice was added to form the octahydrate of thorium sulfate. The solution was then transferred to a large centrifuge tube, made alkaline to phenol red with concentrated ammonium hydroxide and allowed to stand for thirty minutes. The precipitate of thorium was then centrifuged for ten minutes, the supernatant fluid discarded and the precipitate washed with water and centrifuged again. The precipitate was then dissolved in 1 or 2 drops of concentrated hydrochloric acid and transferred to a 15 cc. narrow-tipped centrifuge tube; 1 cc. of 10 per cent oxalic acid was added and the mixture placed in the ice box over night. The

14. Angermann, M., and Overhof, K.: Ztschr. f. d. ges. exper. Med. **94**:121, 1934.

15. The preparation used was thorotrast, manufactured by the Heyden Chemical Corporation, 50 Union Square, New York, and contained 24 to 26 per cent thorium dioxide by volume.

16. Schoeller, W. R., and Powell, A. R.: The Analysis of Minerals and Ores of the Rarer Elements, Philadelphia, J. B. Lippincott Company, 1919, p. 104.

thorium oxalate precipitate was then washed three times with water, care being taken in decanting the supernatant fluid, and then titrated at 90 C. with hundredth-normal potassium permanganate. During the chemical procedure, traces of iron and calcium phosphate are carried over with the thorium, and it is necessary to determine the oxalate equivalent by making a blank determination of the plasma content before the injection of thorium dioxide; this equivalent is deducted from the total amount of permanganate used. The blank value varied from 0.07 to 0.13 cc. of hundredth-normal potassium permanganate. The calculation, then, is: One cubic centimeter of hundredth-normal potassium permanganate equals 0.66 mg. of thorium dioxide. The error of the method is less than 5 per cent.

The rate of removal of thorium was determined for dogs anesthetized with ether and with intravenously injected pentobarbital sodium (0.025 Gm. per kilogram). The surgical procedures were carried out with the animals under ether anesthesia and with an aseptic technic.

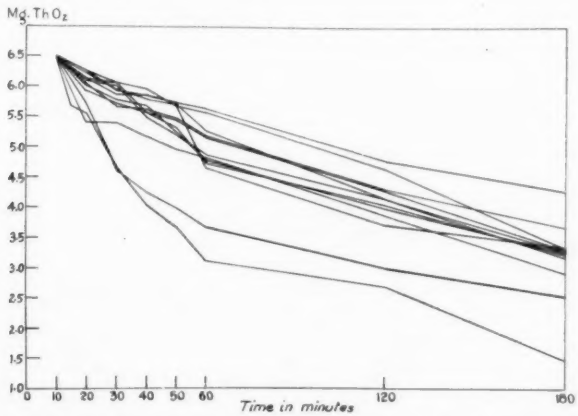

Chart 1.—Curves obtained during a three hour period following injection of thorium dioxide into normal dogs. Values at ten minutes after injection were placed at the same point so that the slope of the curve could be composed.

RESULTS

Normal Dogs.—Two to six curves were obtained for each dog. The curves for 14 dogs showed a similar general slope (chart 1), but in 2 cases the colloid was removed at a faster rate than in the others. The type of curve remained the same for each normal dog for at least two months. The rate of removal was always fastest within twenty minutes after the injection and then became slower. For 4 dogs a flat region in the curve was detected between twenty and forty minutes after the injection. Thorium was found to disappear completely from the blood between ten and twelve hours after the injection. While the slope of the curve remained the same for any normal dog, the absolute values

of thorium differed slightly, depending probably on the differences in the volume of the blood from day to day.

Anesthesia.—No changes were detected in the curves of thorium removal after ether or pentobarbital sodium anesthesia (chart 2). No attempt was made to keep the body temperature at a normal level, and a decrease in the temperature of 2 to 6 degrees (F.) in the rectum was uniformly found in one hour in dogs anesthetized at room temperature

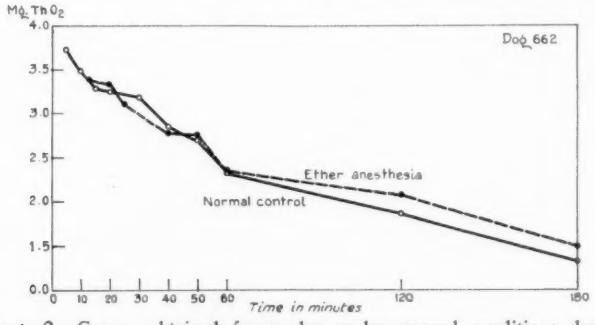

Chart 2.—Curves obtained for a dog under normal conditions during and following ether anesthesia for one hour.

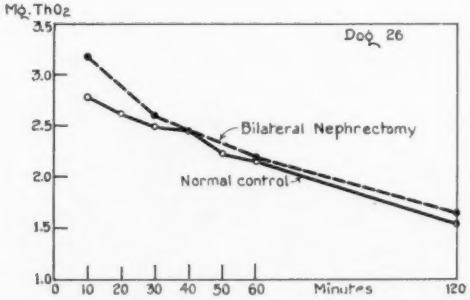

Chart 3.—Curves obtained in a control period and three days following bilateral nephrectomy.

(20 to 25 C.). A decrease in body temperature thus did not affect the velocity of removal with the animal under anesthesia.

Bilateral Nephrectomy.—No changes occurred in the curve (chart 3) even four days after the operation, when there was severe uremia.

Splenectomy.—This operation, carried out on 4 dogs, increased the removal slightly in each case. In 3 cases the curve had returned to normal in forty-eight hours and in 1 case (chart 4) six days after operation.

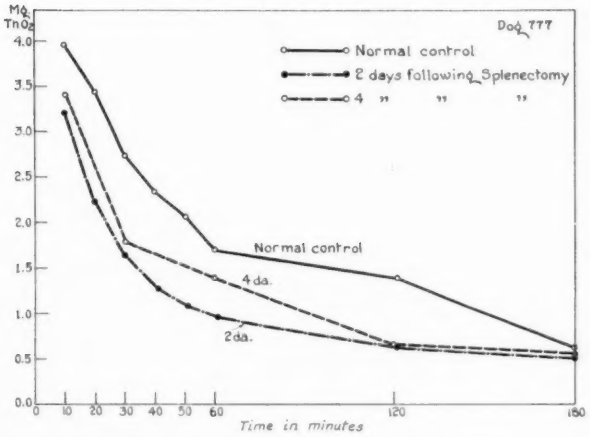

Chart 4.—Normal and postsplenectomy curves.

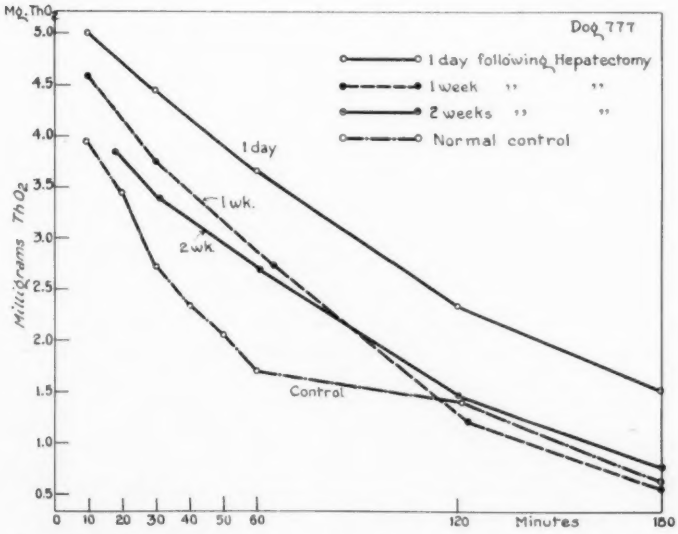

Chart 5.—Curves obtained during a control period and after surgical removal of 34 per cent of the liver.

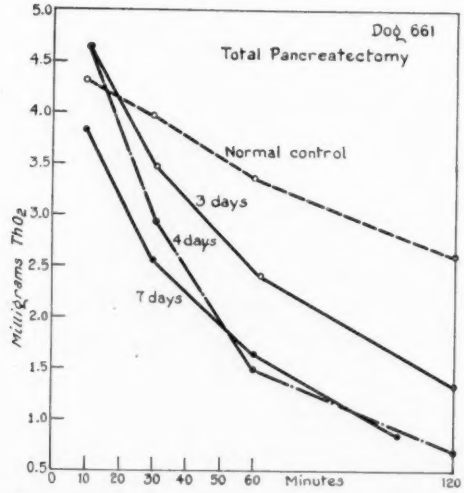

Chart 6.—Normal and postpancreatectomy curves showing the removal of thorium dioxide from the blood.

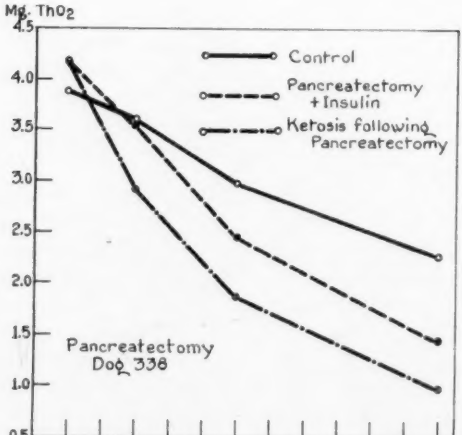

Chart 7.—A normal control curve and postpancreatectomy curves with and without control of ketosis and glycosuria with insulin.

Partial Hepatectomy.—From 4 dogs the largest, left lobe of the liver was removed, and from 2 of these a large right lobe was also removed. By comparing the weight of the liver removed to the weight of the liver remaining at autopsy, 19.8 to 36 per cent of the liver was removed. Thorium curves were plotted one, two, four, seven and fourteen days after the operation. In all cases the rate of removal was slowed on the first and second days. For 2 dogs the curve had returned to normal after seven days and for all dogs fourteen days after partial hepatectomy (chart 5).

Total Pancreatectomy.—The pancreas was removed from 5 dogs. Insulin was not given for eight days. Four dogs died between the fifth and the seventh day following operation; 1 dog was studied for forty-two days. At least two thorium-curves were obtained after operation for each dog. In all cases an increased rate of removal occurred (charts 6 and 7). The diabetes was controlled in 1 dog by means of injections of protamine insulin, and curves were obtained during alternating periods of control of glycosuria and ketosis. During the periods of ketosis the rate of removal was always faster than during the control periods, although no final opinion can be drawn from a single case. The total lipid content of the blood was found to be increased 0.2 to 0.45 Gm. over that for the control period, at a time when increased removal was occurring.

COMMENT

The most interesting findings derived from these data seem to be the great functional reserve of the reticuloendothelial system and the difficulty of greatly interfering with the capacity of its cells. The absence of an effect two days or more after splenectomy is in agreement with the findings of Klein and Levinson [12a] and of Mills and Dragstedt,[12b] who found slight or no changes in the rate of removal of bromsulphalein from splenectomized dogs, although a recognizable fraction of this "system" had been removed. Removal of about one quarter of the liver, however, did slow the removal rate for a few days.

It is well known that in dogs that have undergone total pancreatectomy, purulent conjunctivitis and wound and other infections are more likely to develop than in nondiabetic dogs. The finding that particulate matter is removed at a faster rate from diabetic dogs than from normal animals is of interest in connection with this decreased resistance to infection and indicates that the ability of the macrophages to ingest particles is not the cause of the disturbance.

SUMMARY AND CONCLUSIONS

The curves for the removal from the blood of injected colloidal thorium dioxide were similar for 14 dogs, but in 2 cases the velocity

was appreciably faster. This colloid is removed fastest during the first twenty minutes after injection, then at a slower rate, until it disappears from the blood between ten and twelve hours, with the doses used. The rate of disappearance of thorium was not significantly affected by ether or pentobarbital sodium anesthesia, by bilateral nephrectomy or by splenectomy. The rate slowed after the removal of about one quarter of the liver and was increased during the diabetes following pancreatectomy.

The evidence shows that the decreased resistance to infection of diabetic dogs is not caused by an inability of macrophages to ingest large particles, such as bacteria.

Dr. Lillian Eichelberger and Dr. Paul B. Donovan gave advice and assisted in this study.

INTUBATION OF THE HUMAN SMALL INTESTINE

XII. THE TREATMENT OF INTESTINAL OBSTRUCTION AND A PROCEDURE FOR IDENTIFYING THE LESION

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Intestinal intubation [1] may now be regarded as an established clinical procedure. It has been employed in more than five hundred instances in the clinic of the Hospital of the University of Pennsylvania and to a less extent in a number of other institutions in this country and abroad. The technic is time consuming and may be difficult even for the experienced worker. The results obtained in the management of intestinal obstruction alone, however, seem to justify its inclusion among the procedures available in all large general hospitals. The employment of the method in 16 cases of acute obstruction has previously been described (Abbott and Johnston [2]), but further experience has indicated in more detail the various ways in which the method is therapeutically and diagnostically helpful in such cases. It may be utilized advantageously throughout the acute phases of the patient's illness and its beneficial effects include, in chronologic order, the possibilities (*a*) of emptying the intestine and restoring peristalsis, (*b*) of supplying promptly the data needed in the adjustment of the fluid and electrolyte balances of the body, (*c*) of relieving the obstruction itself, (*d*) of identifying the location and nature of the lesion, (*e*) of simplifying the technic of any required surgical procedure, (*f*) of protecting the suture line after operation and (*g*) of converting an emergency into an elective surgical procedure.

Aided by a grant from the Committee on Scientific Research of the American Medical Association.

From the Gastrointestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of the University of Pennsylvania.

Presented before the Fifty-Fifth Annual Meeting of the American Clinical and Climatological Association, Atlantic City, N. J., on May 4, 1938.

1. Miller, T. G., and Abbott, W. O.: Intestinal Intubation: A Practical Technique, Am. J. M. Sc. **187**:595-599 (May) 1934.

2. Abbott, W. O., and Johnston, C. G.: Intubation Studies of the Human Small Intestine: X. A Non-Surgical Method of Treating, Localizing and Diagnosing the Nature of Obstructive Lesions, Surg., Gynec. & Obst. **66**:691-706 (April) 1938.

TECHNIC

The technic of intubation of the obstructed intestine is the same as that already described for the normal [1] and for the obstructed bowel.[2] It may be carried out with any apparatus which includes (1) a rubber tube for the aspiration of intestinal contents, (2) a thin rubber balloon at the end of the tube for engaging peristalsis and (3) a fine rubber tube for inflating the balloon. Either a tube with a double lumen or a large and a small tube tied together will suffice (fig. 1). An opening, for the aspiration of contents, is often placed distal to the balloon, thus facilitating decompression ahead of the instrument. Preferably, because the tube at times must be kept in place for several days, the apparatus should be introduced through the nose. The balloon must never be inflated until it has entered the duodenum, for a full balloon will not leave the stomach. In the absence of a fluoroscope with which to identify the location of the tube, since gastric and duodenal contents in the obstructed intestine are often indistinguishable, the presence of the tip of the tube in the duodenum may be determined by the feel of the syringe plunger as the initial 10 cc. of air is injected into the balloon, the gentle, rhythmic resistance of the duodenum contrasting sharply with the lack of all sense of resistance when the balloon lies in the stomach. If the tip has not advanced sufficiently, this inflation may cause it to be regurgitated back through the pylorus; but if it is well placed, the balloon will advance rapidly, and the patient will perceive that the tube is slipping more easily down his throat as the intestine starts propelling the balloon.

THE ADVANTAGES OF INTUBATION AS AN ADJUNCT IN THE TREATMENT OF INTESTINAL OBSTRUCTION

(*a*) *The Intestine Can Be Decompressed and Peristalsis Restored.*—This fact has been repeatedly manifested. It has been shown (Abbott, Zetzel and Glenn [3]) that peristalsis is first rendered more effective and then abolished by progressive distention and that in the presence of mechanical obstruction a zone of absent peristalsis, preceded by a zone of hyperperistalsis, extends progressively orad from the point of blockage. Until death of the muscularis results, this process is reversible. Thus a patient who has had an obstruction for a long time and who presents great distention of the abdomen, with no audible peristalsis, or one who has shown paralytic ileus from the start may undergo intubation successfully because, as the stomach, the duodenum and the subsequent sections of small bowel are deflated, each in turn regains its peristaltic activity and forces the balloon onward. As this takes place the patient experiences striking relief of pain and abatement of his shocklike symptoms, the normal motor function of the intestine being at the same time restored.

Reverse peristalsis distal to the duodenum has not as yet been observed in any case, the orad flow of intestinal contents resulting from

3. Abbott, W. O.; Zetzel, L., and Glenn, P. M.: Observations on the Motor Activity of the Obstructed Small Intestine Made During the Course of Treatment by Intubation, Am. J. M. Sc. **195**:279-280 (Feb.) 1938.

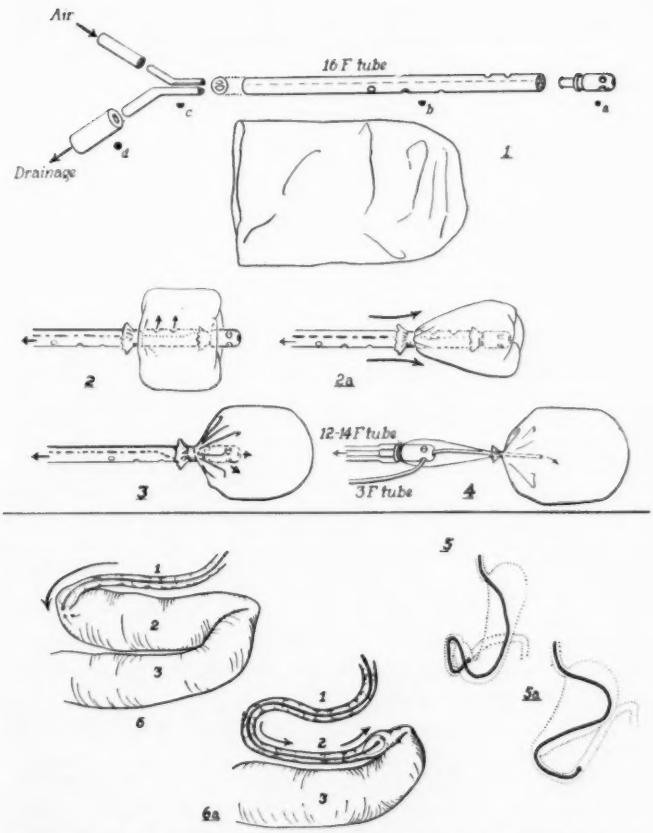

Fig. 1.—Technic of Intubation: *1*, the component parts of a tube for the small intestine; *a*, the aspirating tip, size 16 F; *b*, double-lumened tube with perforations from the small lumen for inflation of the balloon and into the large lumen for aspiration of intestinal contents; *c*, metal connections; *d*, round rubber tubing connecting the apparatus to aspirating bottles or to a syringe for the injection of air (the rubber balloon is cut to the correct size before being tied on the tube). It is of great importance in assembling a tube to safeguard against blockage by seeing that the diameter of the lumen of every part from tip to bottle increases progressively. *2*, the tube assembled for aspiration both ahead of and behind the balloon. In *2a* is shown the importance of a loose balloon that can sag forward, temporarily covering the tip as it advances. *3*, the tip is mounted on the small lumen so that the balloon precedes the tube, an assembly that is particularly useful in the presence of multiple adhesions. *4*, the balloon on a separate tube draws a single-lumened aspirating tube after it, a device used chiefly in cases of multiple partial obstructions. *5* and *5a*, the fluoroscopic appearance of tubes at the point in the duodenum at which the balloon may safely be inflated without fear of its being regurgitated back into the stomach. *6* and *6a*, the way in which a tube is believed to empty the intestine, segment by segment, deflating it, allowing the blood supply to return and then being advanced to the next point of angulation by the returning peristalsis.

hypersecretion above the obstruction, as described by Herrin and Meek,[4] while peristalsis, rendered incompetent by the dilatation of the intestine, behaves, as Brinton[5] described it, like a hollow piston in a cylinder without an outlet. It has frequently been contended that suppression of peristalsis is a toxic manifestation (which in some instances it may be), but the following case is an instance in which overwhelming toxemia failed to prevent the restoration of peristalsis after satisfactory decompression.

H. X., a woman of 41 years, was in good health until the abrupt onset of severe abdominal pain. Twenty-four hours later she was admitted to the service of L. D. Englerth, and at operation volvulus of the cecum and the terminal portion of the ileum was present. The loop of bowel was gangrenous and had ruptured, spilling feces throughout the peritoneal cavity. The stumps of the ileum and cecum were exteriorized, and the pelvis was drained. At first the abdominal symptoms were controlled by Wangensteen drainage, but six days after operation distention of the bowel suddenly became marked and her temperature rose sharply. On the seventh day, though the patient was critically ill and had no audible peristalsis, intubation was performed. She died of general peritonitis thirty-six hours later, but for the last twenty-four hours of life peristalsis was active, the abdomen was flat and feces were discharged through the stump of the ileum.

(*b*) *The Control of the Fluid and Electrolyte Content of the Body Is Facilitated.*—On admission the patient with critical obstruction is likely to present a state of shock. The extremities are cold and blue, and the pulse is rapid and thready. The relief of pain that comes with intestinal decompression may improve the situation markedly, but the fundamental chemical imbalance, as a rule involving water, electrolytes and serum protein, must be corrected as rapidly and accurately as possible if the patient is to survive. The work of Hartwell and Hoguet,[6] of Haden and Orr[7] and of many others has shown the character of the deviations from normal to be expected, but the great practical difficulty in accurate replacement therapy has always depended, in the first place, on the delay in securing a report on the chemical examination of the blood and, in the second place, on the rapidity with which the state of the patient changes. In a word, successful maintenance of a patient with obstruction depends on a reasonably accurate estimation of his needs in terms of fluid, electrolytes and plasma protein almost from hour

4. Herrin, R. C., and Meek, W. J.: Distention as a Factor in Intestinal Obstruction, Arch. Int. Med. **51**:152-168 (Jan.) 1933.

5. Brinton, W.: Intestinal Obstruction, edited by T. Buzzard, London, John Churchill & Sons, 1867.

6. Hartwell, J. A., and Hoguet, J. P.: Experimental Intestinal Obstruction in Dogs, with Especial Reference to the Cause of Death and the Treatment by Large Amounts of Normal Saline Solution, J. A. M. A. **59**:82-87 (July 13) 1912.

7. Haden, R. L., and Orr, T. G.: Chemical Changes in the Blood of the Dog After Obstruction of the Duodenum, J. Exper. Med. **37**:365-375 (March) 1923.

to hour at the start. Intubation permits such determinations because it allows one to measure exactly the loss of fluid from the body into the intestine, otherwise impossible; and since the salt content of such fluid is approximately that of the blood plasma, one can, by making adjustments for the fluid taken by mouth, estimate roughly the amount of sodium chloride needed. The following cases indicate certain of these fluid and electrolyte relations.

S. W., a man aged 75 years, was in good health until a sharp pain occurred in the right lower quadrant of the abdomen. Three days later, after much colicky pain and distention, he was admitted to the service of E. L. Eliason, and a ruptured appendix with a pericecal abscess was present at operation. By the second postoperative day the intestinal obstruction was the major problem. The patient was drowsy and somewhat dehydrated; the abdomen was distended, peristalsis was inaudible and vomiting was occurring intermittently. The chloride content of the plasma was 91 milliequivalents per liter. Intubation was performed, and the patient was given liquids by mouth as the tube went down the intestine. Though his condition seemed critical, he improved rapidly and on the fourth day after operation was alert and in good condition. On the fifth day he complained of pain in the chest. Fever rapidly developed, and death due to bronchopneumonia occurred on the sixth day after operation. Table 1 indicates the relative constancy of the sodium chloride concentration in the intestinal drainage in this case, in spite of the rather wide variations in the amount and in the route of the water and fluid received together with the large volume recovered by drainage.

In contrast is the case of E. H., a woman of 53 years, admitted to the service of E. L. Eliason, who was operated on for annular carcinoma of the rectosigmoid flexure. The first stage of a Mikulicz operation was performed, followed in two days by the second stage. On the day following the latter procedure, marked distention set in, unrelieved by Wangensteen drainage. On the fifth day after the original operation, intubation of the jejunum was done. On the ninth day, her condition being greatly improved, the third stage of the operation was performed, the tube was withdrawn and uneventful convalescence followed.

Table 1 shows data on the intake and output of salt and fluid in 2 cases. From this it appears that within wide limits the concentration of salt in the drainage is unaffected by the salt content and the volume of fluid ingested. The observed range being so narrow, one can estimate closely the amount of sodium chloride lost in the drainage and can replace a comparable amount within a few hours. This is a real help in avoiding not only hypochloremia but also the possibility of hyperchloremia, with mucosal edema which might in turn increase the obstruction.

(*c*) *Relief of the Obstruction Is Obtained by Intubation.*—Wangensteen [8] has pointed out that decompression of the stomach and duodenum will occasionally result in the relief of the obstruction itself. This is

8. Wangensteen, O. H.: The Therapeutic Problem in Bowel Obstructions: A Physiological and Clinical Consideration, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

TABLE 1.—*Clinical Data for Two Patients*

Clinical Data				Intake						Intestinal Drainage			
				Fluid, Cc.			Salt, Gm.						
Patient	Period of Obstruction, Days	Position of Tube	Time Interval	Mouth	Vein	Total	Mouth	Vein	Total	Volume, Cc.	Sodium Chloride, Gm.	Rate of Flow, Cc./Hr.	Concentration of Sodium Chloride, Gm. per 100 Cc.
S. W.	2	Jejunum	2:00 p.m. - 7:00 p.m.	1,045	1,000	2,045	...	9.0	9.0	1,850	9.9	370	0.54
		Jejunum, low	7:00 p.m. - 12:00 p.m.	780	.....	780	...	....	....	1,850	7.0	370	0.37
		Ileum, high	12:00 p.m. - 6:00 a.m.	1,380	.....	1,380	...	....	....	1,800	7.0	300	0.37
			16 hours.....	3,205	1,000	4,205	...	9.0	9.0	5,500	23.9	343	0.43
	3	Ileum	6:00 a.m. - 1:30 p.m.	1,435	1,000	2,435	...	9.0	9.0	1,700	6.2	223	0.52
			1:30 p.m. - 6:30 p.m.	1,090	833	1,923	1.0	6.1	7.1	1,425	8.1	283	0.57
			6:30 p.m. - 2:00 a.m.	2,050	.....	2,050	...	....	....	1,850	9.3	246	0.50
			2:00 a.m. - 7:00 a.m.	1,000	.....	1,000	...	....	....	1,100	4.2	220	0.38
			25 hours.....	5,575	1,833	7,408	1.0	15.1	16.1	6,075	27.8	243	0.46
	4	Ileum, low	7:00 a.m. - 1:30 p.m.	1,395	1,000	2,395	0.6	9.0	9.6	1,700	9.4	261	0.55
			1:30 p.m. - 7:00 p.m.	1,380	1,300	2,680	6.5	24.0	32.5	1,500	11.8	273	0.79
			7:00 p.m. - 6:00 a.m.	2,640	1,300	3,940	...	10.5	10.5	1,850	9.9	168	0.54
			23 hours.....	5,415	3,600	9,015	7.1	43.5	52.6	5,050	31.1	219	0.62
	5	Ileum, low	6:00 a.m. - 12:00 a.m.	1,810	1,000	2,810	0.6	9.0	9.6	1,800	8.4	300	0.46
			12:00 a.m. - 6:00 p.m.	600	1,000	1,600	...	7.8	7.8	1,325	6.0	221	0.49
			6:00 p.m. - 6:00 a.m.	1,830	1,500	2,330	...	13.5	13.5	1,850	10.5	154	0.56
			24 hours.....	4,240	3,500	6,740	0.6	30.3	30.9	4,975	24.9	235	0.50
	6	Ileum, low	6:00 a.m. - 2:00 p.m.	1,090	1,000	2,090	1.0	9.0	10.0	1,800	8.38	222	0.46
		Died three hours later of bronchopneumonia; last specimen lost											
E. H.	5	Stomach to jejunum	7:00 a.m. - 7:00 p.m.	540	1,000	1,540	0.2	9.0	9.2	420	2.5	35	....
			7:00 p.m. - 6:00 a.m.	840	1,000	1,840	1.0	9.0	10.0	500	2.2	45	0.44
			23 hours.....	1,380	2,000	3,380	1.2	18.0	19.2	920	4.7	40	....
	6	Ileum	6:00 a.m. - 6:00 p.m.	470	1,000	1,470	0.5	6.0	6.5	1,900	10.4	157	0.55
			6:00 p.m. - 7:00 a.m.	310	1,000	1,310	0.9	9.0	9.9	875	6.9	67	0.79
			25 hours.....	780	2,000	2,780	1.4	15.0	16.4	2,775	17.3	112	0.67
	7	Ileum	7:00 a.m. - 7:00 p.m.	1,800	2,500	4,300	0.5	22.5	23.0	1,700	11.2	141	0.66
			7:00 p.m. - 7:00 a.m.	880	2,000	2,880	1.5	9.0	10.5	825	5.5	69	0.66
			24 hours.....	2,680	4,500	7,180	2.0	31.5	33.5	2,525	16.7	105	0.66
	8	Ileum	7:00 a.m. - 7:00 p.m.	1,620	3,925	5,545	0.7	35.1	35.8	1,250	5.49	104	0.47
			7:00 p.m. - 7:00 a.m.	1,480	1,650	3,130	...	15.3	15.3	1,700	11.0	104	0.73
			24 hours.....	3,100	5,575	8,675	0.7	50.4	51.1	2,950	16.5	104	0.60
		Intestinal activity returned; tube was withdrawn; convalescence was uneventful											

seen even more often after aspiration of the contents of the entire small intestine above a lesion. In a patient with temporary obstruction due to a local inflammatory raction, the condition will sometimes subside if he can be kept alive long enough. When relief occurs, it is presumably the result of collapsing the intestine and of diverting the intestinal current, thus promoting free movement of the coils in the abdomen and subsidence of local inflammatory edema. In some instances it is advisable subsequently to operate and to remove the abnormal structure, but in many instances the primary factor is a multiplicity of operations in the past. Even though another episode of obstruction may occur in a day or a year, it is desirable, when possible, to avoid the trauma of another laparotomy, as illustrated by the following case:

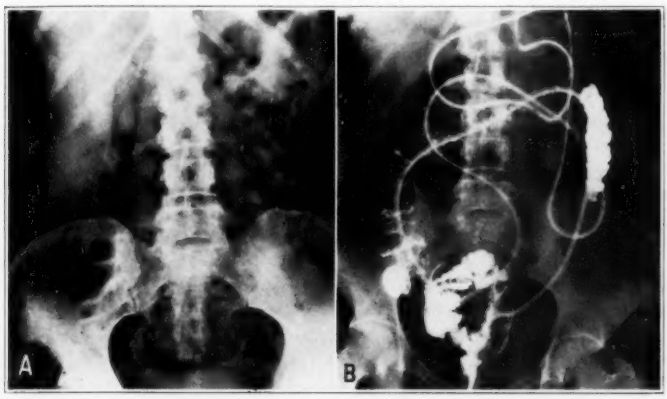

Fig. 2.—Relief of an obstruction caused by postoperative adhesions. V. I., a patient aged 47, had been obstructed for six days. *A*, showing the distention of the abdomen on entry. The intestine being largely distended with fluid, only small collections of gas can be seen in the small intestine. *B*, the balloon has been expelled through the rectum, having passed through the entire alimentary canal.

V. I., a woman of 47 years, had undergone a pelvic operation ten years earlier which left her with a tendency to constipation and the passage of flattened stools. Thinking that she was again constipated, she allowed four days to pass without a stool, but by the sixth day colicky abdominal pain and increasing distention led to her admission to the service of I. S. Ravdin. Although once or twice the passage of a drachm (4 Gm.) of feces occurred, she presented clinical signs of mechanical obstruction and roentgenographic evidence of gas in the small intestine (fig. 2). A tube was passed, and it advanced until the balloon lay in the ascending colon. The distention was relieved, and peristalsis was again normal. A barium sulfate enema was given at this time, and when the enema fluid was expelled, the balloon and a foot (30 cm.) of tube were passed by rectum. Subsequently, though the acute obstruction was relieved, an operation was necessary to sever adhesions about the rectosigmoid flexure.

(*d*) *Roentgenographic Study of the Lesion Is Possible.*—There are few who have the temerity to give a barium sulfate meal to a patient with acute obstruction, yet 50 or 100 cc. of a dilute suspension of barium sulfate can safely be injected by tube: (*a*) because it can be withdrawn again if the obstruction is complete and (*b*) because in a mechanically obstructed intestine, since the balloon goes actually to the obstruction, much can be learned from a minimal amount of opaque medium. This may be exemplified by the following case:

F. D., a man of 36 years, had been ill for nine years, the diagnoses being tuberculous enteritis, regional ileitis, appendicitis and ulcerative colitis. Five abdominal operations had been performed during that period. He was admitted to the service of I. S. Ravdin after seven days of partial obstruction and after three days of complete obstruction. Distention was marked, fecal vomiting was incessant and each bout of retching ended in a tetanic spasm. The cold, blue extremities and rapid, thready pulse indicated a marked degree of shock (fig. 3). A tube was at once placed in his stomach. Twelve hours later it had started down the small intestine. The fluid output approximated 6 liters a day for the first forty-eight hours and was balanced by fluids given intravenously, including blood and the required electrolytes. In thirty-six hours he was comfortable and sitting up in bed. On the third day of the patient's hospitalization the tip of the tube was observed fluoroscopically to lie in the right lower quadrant of the abdomen. A thin suspension of barium sulfate, totaling 50 cc., was injected, and films were exposed. From this study it was determined that excision of the right side of the colon, with an ileocolostomy opening to the mid portion of the transverse colon, had been done previously. An intrinsic constricting lesion of the terminal 6 inches (15 cm.) of ileum was producing the obstruction; and although adhesions were present, it was felt that the lower portion of the ileum was free enough to permit a new ileocolostomy. This was carried out. The diseased tissue, which proved to be due to a recurrence of regional ileitis, was excised, and a satisfactory convalescence resulted, the tube being withdrawn on the third postoperative day (fig. 4).

(*e*) *The Surgical Technic Is Simplified.*—This is obviously true when one considers the difficulty of operating on a patient with thin-walled, distended intestines which are constantly threatening to extrude from the wound, in contrast to operating on a patient who arrives in the operating room with a flat abdomen and empty intestines; but even when preoperative decompression is incomplete because of multiple obstructions, the technic is still simplified, because by manipulating the tube at operation, the surgeon may be able to place its tip in one obstructed area after another until complete decompression is accomplished.

A. H., a man of 63 years, was well until abdominal pain with constipation developed. During the first twenty-four hours the pain increased, and he took laxatives. After five days without a bowel movement, he was admitted to the service of I. S. Ravdin, with clinical signs of mechanical intestinal obstruction. The tube passed down the small intestine, but incomplete relief of distention resulted (fig. 5). At operation on the fifth day following hospitalization, two

long-distended loops of intestine bulged from the wound. Three bands of adhesions were present, the first having stopped the tube. With the balloon deflated, the surgeon passed the tip of the tube under the first and then the second adhesion, the loops being emptied by means of a syringe applied to the proximal end of the tube. With the collapse of the distended intestine, the dissection of the adhesions and the replacement of the loops in the abdomen were greatly facilitated. Convalescence was uneventful.

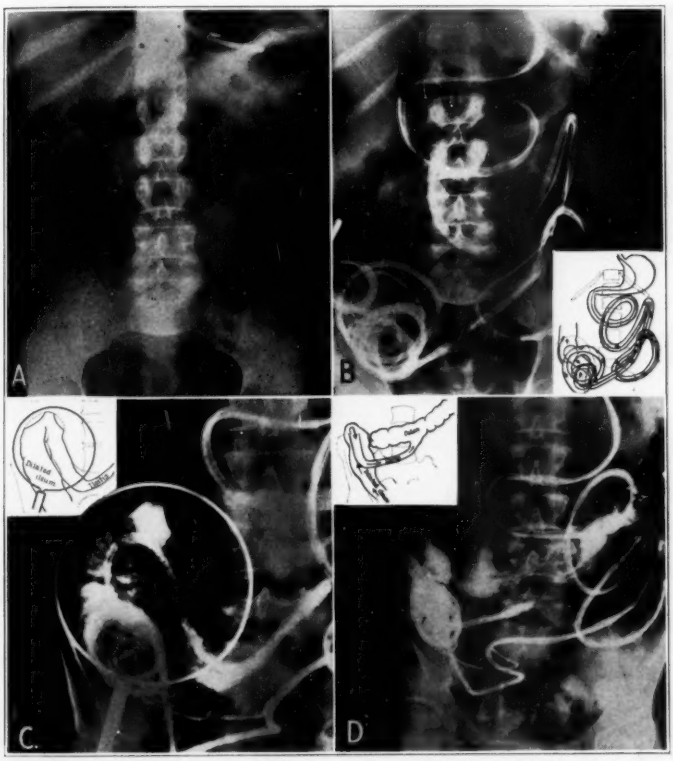

Fig. 3.—The injection of barium sulfate for diagnostic purposes. F. D., aged 36, had had partial obstruction for seven days and had had complete obstruction for three days due to recurrence of regional ileitis. *A*, showing distention of the small intestine with gas and fluid. The tube is entering the stomach. *B*, the tip lies in the right lower quadrant of the abdomen, with the tube coiled behind it in the dilated ileum. *C*, after the injection of 50 cc. of a thin barium suspension and the application of pressure. The adhesions, pinning out the ileum, are apparent, together with the abrupt transition from dilated to constricted intestine. The tube, with the balloon deflated, has entered the constricted segment. *D*, barium has entered the colon, indicating (*a*) the site of the old ileocolostomy, (*b*) the length of the segment of ileum in which the ileitis has recurred and (*c*) the stump of transverse colon, demonstrating that the ascending colon had been excised.

(*g*) *Protection of the Suture Lines Results.*—A tube in the intestine protects the suture line of an anastomosis from internal pressure. Frequently in cases of long-standing partial obstruction, as in acute complete obstruction, the intestine above the blockage is thin as paper, and the danger of leakage through the suture line, if resection is attempted, is far greater than after operations on more normal tissue.

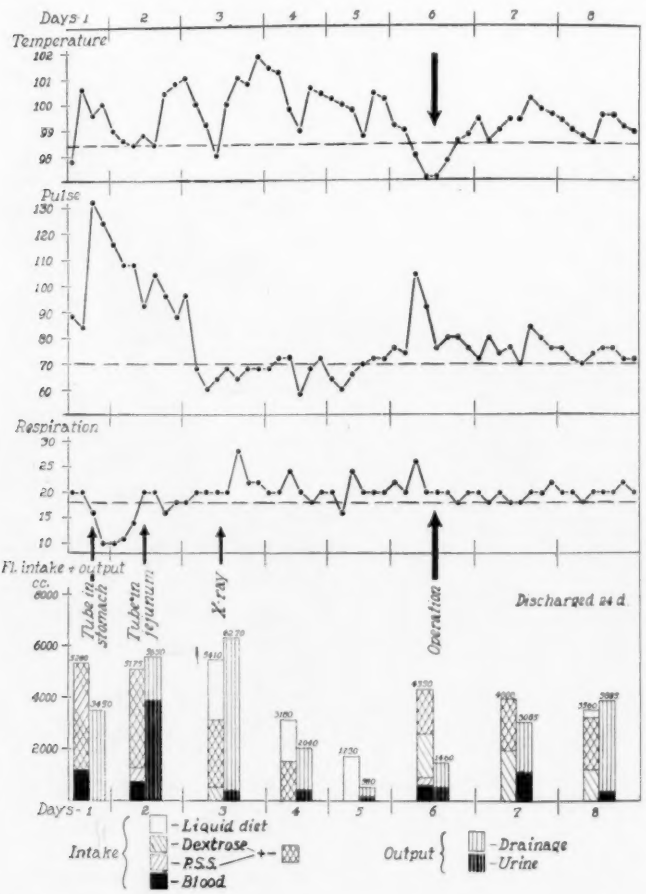

Fig. 4.—Acute intestinal obstruction. F. D., aged 36, had recurrent regional ileitis. He was admitted to the hospital seven days after the first attack of colic and three days after obstruction became complete. The temperature, pulse rate and respiration rate during treatment by means of intubation; roentgenographic studies, and finally resection of the diseased area, with the construction of a new ileocolostomy opening, are shown.

If there is a tube in the intestine above the point of operation during the early part of convalescence, it is possible to keep this part of the intestine empty, even though small amounts of fluid and food are taken by mouth from the day of operation. This was exemplified in the following case:

S. B., a man of 20 years, had been admitted to the service of I. S. Ravdin thirteen times in two years for the relief of regional ileitis and its complications. On his last entry he weighed only 70 pounds (31.8 Kg.) and had six fecal fistulas to different points on the abdominal wall and signs and symptoms of chronic intestinal obstruction. Previously appendectomy and ileocolostomy at the mid-portion of the transverse colon had been done. The terminal portion of the ileum and the cecum, however, had been left in place. Intubation was requested in an effort to locate the point of obstruction and the points of origin of the fistulous tracts. The tube was passed as far as it would go. Barium sulfate was injected into

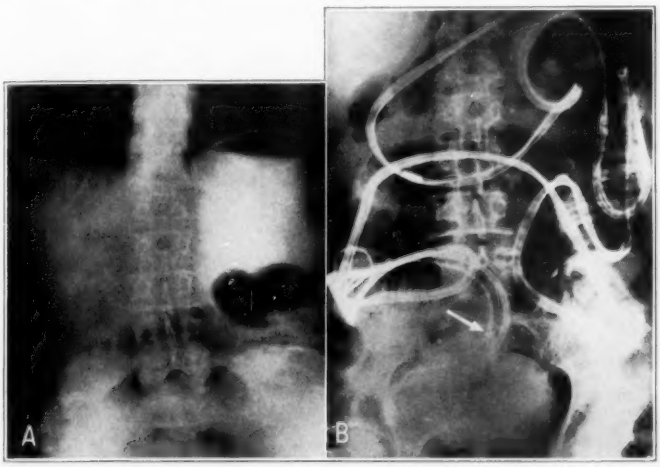

Fig. 5.—Incomplete decompression in the presence of multiple obstructions. *A*, a roentgenogram taken on entry, showing gastric dilatation and a collection of gas in the small intestine. *B*, after intubation and the injection of barium sulfate the opaque material can be seen to have entered a distended segment of intestine distal to the tip of the tube (arrow).

the terminal portion of the ileum and by catheter into the fistulas, while small amounts of barium were given in an enema. It became apparent that the cecum, ascending colon and half the transverse colon had contracted to form a fibrous pouch, about 15 cm. in length, in the right lower quadrant of the abdomen into which all the fistulas led (fig. 6). From this scarred area, fairly normal colon passed diagonally upward to the splenic flexure, while in the area of the ileocolostomy the intestine was markedly obstructed by bands of scar tissue, thus producing huge dilatation of the lower portion of the ileum. By manipulation of the tube it was determined that these coils were freely movable and that a new ileocolostomy was practicable. This was done. The colon and terminal portion of

the ileum were transected, and the ends toward the diseased area were turned in and oversewed, while the dilated end of the ileum was anastomosed to the left side of the transverse colon. The danger of operating on such an ill patient was appreciated, especially in view of the fact that the fecal fistulas were constantly contaminating the abdominal wall; but the chief concern was for the ileocolostomy anastomosis, because the terminal portion of the ileum was almost as thin as paper. The balloon was therefore deflated and then drawn back to a point well above the site of operation. Suction was maintained for three days after operation, and successful convalescence resulted (fig. 7).

(*h*) *Operation Is Delayed.*—Variable as are the enumerated advantages of intubation, there is still one of major and outstanding importance. The passage of a tube to the point of obstruction at once converts

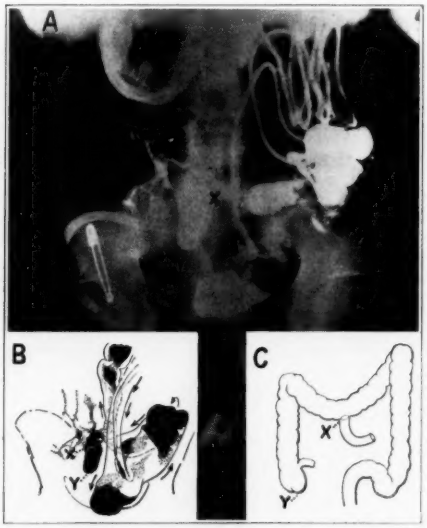

Fig. 6.—Partial obstruction for months due to recurrent regional ileitis (S. B., aged 20). *A*, a roentgenogram taken after the injection of barium sulfate, showing filling of six fecal fistulas and the intestinal tube. *B*, a drawing reconstructing the intestinal relations as interpreted from the roentgenographic study. *C*, a drawing of the colon and ileum as they were left after the original ileocolostomy. The ileum entered the mid portion of the transverse colon by an end to side anastomosis, while the diseased stump of ileum remained in situ. In each figure *X* represents the ileocolostomy opening and *Y* the head of the cecum. It was apparent that the entire cecum, ascending colon and part of the transverse colon had contracted to form a chamber, between 10 and 15 cm. in length, into which all the fistulas emptied. The obstruction was due to constriction of the ileum at the site of the ileocolostomy. By manipulation of the coils of intestine containing the tube it became evident that there was sufficient motility to bring sound ileum and colon together for a new ileocolostomy opening.

a situation calling for emergency measures into one in which the time of operation, if it is performed at all, becomes a matter of election. The great contraindication to intubation is the presence of gangrenous tissue. When that is absent, intubation temporarily controls the situation. One's success with the procedure, therefore, will be no better than one's clinical judgment. In cases of external hernia intubation is not necessary; likewise, in cases of low colonic obstruction, save in special instances. There remain occasional strangulated internal hernia, volvulus,

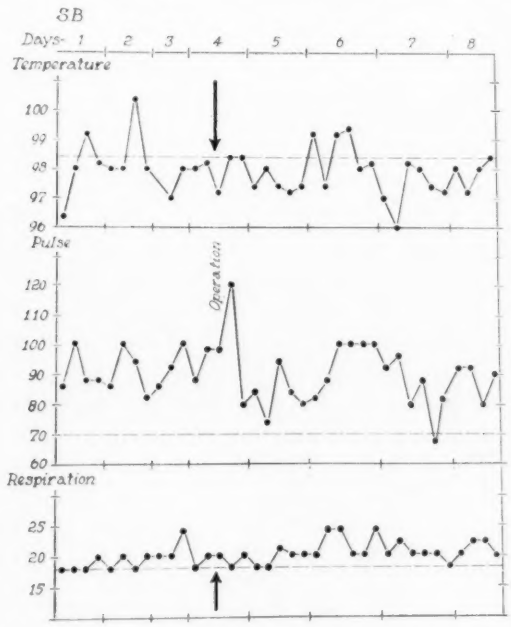

Fig. 7.—The clinical course recorded for S. B. (fig. 6). The curves show the temperature, pulse rate and respiratory rate before and after the performance of ileocolostomy, with exclusion of the cecum. The intestinal tube was left in place so that constant suction could be maintained above the suture line. Since the intestine was thin at the point of anastomosis, the measure proved a real safeguard.

intussusception and mesenteric thrombosis as conditions productive of intestinal infarction. In all of them, however, the severity of the symptoms and the acute localized tenderness are likely to serve as a warning that a blood vessel has been occluded. Granted, however, that in such a case intubation is resorted to, there would be warning of danger by the failure of the symptoms to abate as decompression

TABLE 2.—*Summary of Data*

Case and Initials	Age and Sex	Diagnosis	Duration of Obstruction	Degree of Obstruction	Character of Lesion	Number of Lesions	Duration of Intubation, Days	Operation After Intubation	Period from Admission to Operation, Days	Outcome	Estimated Value of Intubation
					Mechanical Obstruction						
1 H. S.	64 M	Pelvic abscess involving ileum; perforated recto-sigmoid carcinoma	8 days	Complete	Inflammatory swelling of ileum	Single	9	0	..	Recovery	Crucial
2 J. T.	60 F	Rectosigmoid carcinoma	5 days	Complete	Annular carcinoma of sigmoid flexure	Single	6	Yes	6	Recovery	Rendered preliminary cecostomy unnecessary
3 J. R.	68 M	Carcinoma of sigmoid flexure	5± days	Partial	Annular carcinoma of sigmoid flexure	Single	3	Yes	12	Recovery	Very little; cecostomy required
4* D. G.	67 M	Prostatic carcinoma with uremia	2 days	Complete	Massive pelvic lesion	Single	1½	0	..	Death	Symptomatic relief only; death due to uremia
5 J. W.	44 M	Carcinoma of colon with peritoneal carcinomatosis	14 days	Partial	Wide metastases	Multiple	12	0	..	Partial recovery	Tided over acute episode
6 P. B.	50 F	Pelvic adhesions; pneumonia	4 days	Complete	Occlusion of ileum	Multiple	4	0	..	Recovery	Slight; balloon burst
7 S. B.	20 M	Recurrent ileitis with multiple abdominal fistulas	Weeks	Partial	Deformed colon and ileocolostomy	Multiple	4	Yes	Several	Marked recovery	Very great
8 F. D.	36 M	Recurrent regional ileitis in terminal portion of ileum	5 days 3 days	Partial Complete	Constricted terminal portion of ileum	Single	9	Yes	6	Recovery	Crucial
9 A. H.	63 M	Peritoneal adhesions	5 days	Complete	Bands of adhesions	Three	6	Yes	4	Recovery	Very great
10 V. I.	47 F	Pelvic adhesion	6 days	Almost complete	Dense perirectal adhesions	One	3	Yes	5	Recovery	Great
11 F. B.	60± F	Abdominal carcinomatosis	3 weeks	Partial	Diffuse serosal lesions	Multiple	3	0	..	Slow decline	Some symptomatic relief
12 F. N.	40 M	Abscess in abdominal wall	4 days	Partial	Adherence of ileum to abscessed wall	Single	3	Yes	3	Recovery	Great

13* W. S.	47 M	Omental adhesion	3 days	Complete	Ileum occluded by adhesion	Single	1	Yes	..	Recovery	Very great
14 P. I.	28 F	Pelvic adhesion	4 days	Almost complete	Occlusion of ileum	Multiple	2	0	..	Some improvement	Tided over acute episode
15* J. K.	73 M	Colonic carcinoma	4± days	Almost complete	Colonic obstruction	Single	1	Yes	6	Death	Deflated intestine and restored peristalsis
					Paralytic Obstruction						
16* W. S.	47 M	Perforated duodenal ulcer	5± days	Complete	Local peritonitis	.....	7	....	..	Recovery	Crucial
17* F. F.	68 M	Exploratory laparotomy	4 days	Complete	Postoperative ileus	.....	5	....	..	Recovery	Very great
18 H. X.	35 F	Volvulus with ruptured cecum	6 days	Complete	General peritonitis	.....	1½	....	..	Death	Restored intestinal function
19 O. A.	65 M	Intraperitoneal hemorrhage	2 days	Complete	Peritoneal irritation	.....	2	....	..	Death	Slight
20 J. P.	60 M	Prostatectomy; bronchiectasis; bronchopneumonia	4 days	Complete	Postoperative ileus	.....	11	....	..	Death	Restored intestinal function
21 S. W.	75 M	Ruptured appendix; drainage of abscess; bronchopneumonia	2 days	Complete	Postoperative ileus	.....	4	....	..	Death	Partially restored intestinal function
					Failure to Pass the Tube Beyond the Duodenum						
22* W. B.	50 M	Subphrenic abscess; fistulas to abdominal wall and to right bronchus; cicatricial stenosis of duodenum									
23* L. D.	72 F	Femoral hernia surgically corrected; intubation attempted at once without success; no obstruction resulted									
24 M. P.	59 F	Megacolon with low obstruction; tension on gastrocolic omentum prevented intubation									
25 C. R.	63 M	Gastric carcinoma with peritoneal metastasis and multiple obstructions									
26 F. S.	40 M	Postoperative general peritonitis									
27 G. H.	52 M	Metastasis from colonic carcinoma; one mass involved the duodenojejunal junction									

* Cases previously reported.

proceeded, and at any time the decision to operate could be made. On the other hand, when, after intubation in a case of obstruction, the pain and vomiting abate with the disappearance of distention, an enterostomy has been produced above the point of obstruction. True, the enterostomy tube leads through the nose rather than through the abdominal wall, but the advantages and dangers relative to the location, high or low, in the intestines are the same. With the fecal current diverted, a diet of strained soups, fruit juices, eggs, rare beef, farina, boiled or puffed rice, jelly and zwieback or crackers will go far to restore the calories, protein and electrolytes, while the nature of the lesion is being studied. The degree to which this has been possible is exemplified in table 2.

CONCLUSION

From these observations it may be concluded that intubation not only rarely adds to the hazards of acute intestinal obstruction but, on the contrary, frequently improves the clinical condition of the patient, increases his comfort, enables the physician to determine the characteristics of the obstructing lesion, simplifies its resection when that proves necessary, safeguards the convalescence and, above all, contributes to the safety of the patient by converting an emergency condition into a condition that is completely under the physician's control.

Tubing with a double lumen has been made for us by the U. S. Rubber Products Co., Passaic, N. J., and the Lee Tire and Rubber Co., Conshohocken, Pa. A double-lumened tube, fully mounted for intubation of the small intestine, can be obtained through George P. Pilling & Son Co., Philadelphia. A 1/32 inch (1 mm.) tube, suitable for inflating a balloon, is made by the Duval Rubber Co., Providence, R. I.

INFLUENCE OF EXERCISE ON CARDIAC OUTPUT IN CONGESTIVE HEART FAILURE

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CINCINNATI

It has been conclusively demonstrated that the cardiac output of a normal person is increased by exercise.[1] Likewise, in persons with compensated heart disease the occurrence of an essentially normal increase in cardiac output after moderate exercise has been reported by several investigators.[2] Hitherto no studies have been described concerning the influence of exercise on the cardiac output of patients with congestive heart failure. The few studies relating to exercise and its influence on the cardiac output of patients with mild decompensation[3] (able to ride a bicycle or climb stairs) are of doubtful accuracy because of tech-

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1. (*a*) Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932, pp. 129-137. (*b*) Bock, A. V.; Vancaulaert, C.; Dill, D. B.; Fölling, A., and Hurxthal, L. M.: Dynamical Changes Occurring in Man at Work, J. Physiol. **66**:136, 1928. (*c*) Hochrein, M.; Talbott, J. H.; Dill, D. B., and Henderson, L. J.: Die Bestimmung der Blutzirkulation im Ruhe und Arbeit, Arch. f. exper. Path. u. Pharmakol. **143**: 147, 1929.

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3. Bansi, H. W., and Groscurth, G.: Kreislauffunktionsprüfung bei Herzkranken, Deutsche med. Wchnschr. **57**:1276, 1931. Nielsen, H. E.: Clinical Investigations into the Cardiac Output of Patients with Compensated Heart Disease During Rest and During Muscular Work, Acta med. Scandinav. **91**:223, 1937.

nical difficulties inherent in the older methods for determination of the cardiac output in the presence of pulmonary congestion.[4]

Since the inability of a patient with organic heart disease to increase adequately the cardiac output with effort may be an important factor in the pathogenesis of congestive heart failure, we have compared the cardiac output after moderate, measured exercise of (1) patients with congestive heart failure, (2) patients with well compensated heart disease and (3) control subjects.

METHOD

The three sample acetylene method of Grollman as modified by Grollman, Friedman, Clark and Harrison[5] for measurement of cardiac output in cases of congestive heart failure was employed for the determination of the basal cardiac output and the cardiac output following work.

The determinations of cardiac output for the majority of the patients with cardiac decompensation were carried out on the second or the third day after their admission to the hospital, when diminution of dyspnea made cooperation possible. All the patients with congestive heart failure were receiving digitalis. As digitalis has been reported to increase the output of the dilated heart[6] or to have no constant influence on it,[7] the low values for cardiac output obtained for patients suffering from decompensation were probably not related to administration of digitalis.

The patients with compensated heart disease had all suffered from one or more previous episodes of congestive heart failure. The control subjects were of various ages and in varying stages of physical fitness. The patients with cardiac decompensation had entered the hospital because of symptoms of congestive heart failure. Data concerning the patients in the three groups are summarized in the accompanying table.

Each patient was studied under basal conditions. The oxygen consumption was determined with the Benedict-Roth metabolism apparatus while the patient was sitting upright in bed. Relaxation and comfortable position were provided by placing several pillows behind the head and back. After measurement of the basal oxygen consumption, determination of the cardiac output with the patient

4. Grollman,[1a] pp. 48-51.

5. Grollman, A.; Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, J. Clin. Investigation **12**: 751, 1933.

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Patient	Sex	Age	Condition	At Rest: Arterial Blood Pressure, Mm. Hg	At Rest: Pulse Rate	At Rest: Circulation Time, Sec.	At Rest: Vital Capacity, Percentage of Normal	At Rest: Oxygen Consumption per Minute, Cc.	At Rest: Basal Metabolic Rate, Percentage	At Rest: Arteriovenous Oxygen Difference per Liter, Cc.	At Rest: Cardiac Output per Minute, Liters	At Rest: Stroke Volume, Cc.	Work Done, Kilogrammeters per Minute	After Exercise: Arterial Blood Pressure, Mm. Hg	After Exercise: Pulse Rate	After Exercise: Oxygen Consumption per Minute, Cc.†	After Exercise: Arteriovenous Oxygen Difference per Liter, Cc.	After Exercise: Cardiac Output per Minute, Liters	After Exercise: Stroke Volume, Cc.	Increase in Cardiac Output per Minute, Liters
Normal																				
F. F.	♂	56	Peripheral neuritis with foot drop	150/110	84	20	90	236	— 3	56.0	4.22	50	22.2	165/110	90	519	82.5 74.5	6.63	74	2.41
A. N.	♂	47	Convalescent from herniaplasty	110/ 80	78	23	85	204	—10	67.2	3.04	39	18.5	125/ 90	84	268	57.5 53.5	4.81	57	1.77
L. Q.	♂	25	Normal	98/ 78	72	..	96	225	—12	62.3	3.61	50	19.8	110/ 80	96	342	60.3 73.3	5.17	54	1.56
G. S.	♀	30	Neurocirculatory asthenia	110/ 70	84	..	73	185	— 1	52.5	3.53	42	19.8	.....	90	304	58.5 47.7	5.75	64	2.22
F. G.	♂	26	Normal	100/ 70	69	20	113	231	— 4	66.0	3.51	51	19.8	100/ 70	72	386	60.6 70.4	5.91	82	2.40
With Compensated Heart Disease																				
W. P.	♂	50	Arteriosclerotic heart disease with hypertrophy	176/120	72	29	77	288	+24	88.2	3.27	45	19.8	180/130	78	410	73.0 87.0	5.10	65	1.83
W. T.	♂	58	Hypertrophic heart disease	230/ 88	72	17	60	371	+45	75.0	4.95	60	20.4	230/100	66	540	95.0 87.0	5.95	90	1.00
H. M.	♂	31	Rheumatic heart disease; mitral stenosis; aortic insufficiency	110/ 60	96	25	56	234	+25	80.5	2.90	30	20.0	130/ 64	90	304	68.0 77.0	4.20	47	1.30
E. C.	♂	43	Aortic stenosis and insufficiency; mitral stenosis and insufficiency	130/ 30	90	..	84	310	+38	80.0	3.52	39	19.8	180/ 0	114	394	93.5	4.22	37	0.70
With Decompensation																				
E. B.	♂	49	Syphilitic aortitis; aortic insufficiency	140/ 36	96	34	70	250	+12	91.0 88.4	2.79	29	22.2	140/ 48	108	335	93.6 104.0	3.40	31	0.61
A. P.	♂	50	Arteriosclerotic and hypertrophic heart disease	160/130	112	52	36?	231	+30?*	120.3 111.5	2.34	21	19.8	180/140	120	345	113.0 105.0	3.15	26	0.81
H. D.	♂	43	Coronary heart disease	120/100	78	38	53	196	—15	107.0 109.0	1.81	23	19.8	138/100	110	294	110.0 123.0	2.52	23	0.71
M. E.	♀	38	Aortic insufficiency; syphilitic aortitis	126/ 80	126	28	87	186	+ 2	78.5 80.5	2.34	18	20.0	126/ 70	126	257	79.2 83.5	3.16	25	0.82
M. B.	♀	41	Syphilitic and hypertrophic heart disease; general vascular sclerosis	190/ 96	90	..	31?	233	— 5?*	96.0 102.0	2.36	26	18.9	180/ 86	102	328	94.0 113.0	3.19	31	0.83

* Because of peripheral edema the determination of body surface in square meters was approximated.

† Oxygen consumption was measured during, not after, exercise.

at rest was carried out. The subject then remained at complete rest for one-half hour or longer, and a second determination of the oxygen consumption for a three minute period was made.

Both normal control subjects and patients were then required to perform a similar exercise for two minutes. Measurement of oxygen consumption was continued throughout the exercise period. This consisted of lifting in each hand a dumbbell weighing 1½ pounds (0.7 Kg.) to a measured height (97 to 100 cm.) fourteen to eighteen times per minute. The work ranged from 18.5 to 22.2 kilogrammeters per minute. The variable length and weight of the arms were disregarded in calculation of the work performed. This exercise was selected because it was sufficiently mild for patients with congestive heart failure. Moderate dyspnea occurred in each case, but only a slight effect was observed on the frequency and depth of the respirations of the normal subjects.

At the end of the two minute period of work the subject was connected with the portable acetylene apparatus, and the cardiac output was determined. Not more than twenty seconds elapsed in any case between the discontinuation of the work and the beginning of the test. Rapid circulation in the normal group and slow circulation in the group with cardiac disease necessitated collection of the samples at differing times during the experimental procedure. For the patients with cardiac disease our guide for the proper time for collection of samples was the basal circulation time as determined by the sodium cyanide method.

From the normal subjects samples 1, 2 and 3 were collected on the fourth, sixth and eighth expirations, respectively, and the last sample on the fifteenth second of rebreathing. From the patients with compensated heart disease samples 1, 2 and 3 were collected on the fourth, sixth and eighth expirations, respectively, in some cases and on the fifth, seventh and ninth expirations in others, the last sample being obtained between the thirteenth and the nineteenth second of rebreathing. From the patients with decompensation samples 1, 2 and 3 were collected on the seventh, ninth and eleventh expirations in some and on the sixth, eighth and tenth expirations in others and the last sample between the nineteenth and the twenty-third second of rebreathing.

When the arteriovenous oxygen differences between samples 1 and 2 and samples 2 and 3 were within 10 per cent, we assumed that adequate mixing had occurred and that recirculation had not occurred. Occasionally the third sample was collected too late, recirculation having occurred. This became evident if the arteriovenous oxygen difference between samples 2 and 3 was considerably greater than that between samples 1 and 2, and when this occurred the determination was disregarded.

RESULTS

The effects of exercise on cardiac output, stroke volume, oxygen consumption and arteriovenous oxygen difference of the normal subjects, the patients with compensated cardiac disease and the patients with decompensation are summarized in the table. The changes in cardiac output are indicated in charts 1 and 2.

For the controls the average increase in cardiac output following exercise was 2.07 liters per minute; for the patients with compensated heart disease, 1.21 liters per minute, and for patients with decompensation, 0.75 liter per minute. The work performed, as measured in kilogrammeters per minute, was essentially the same for each group.

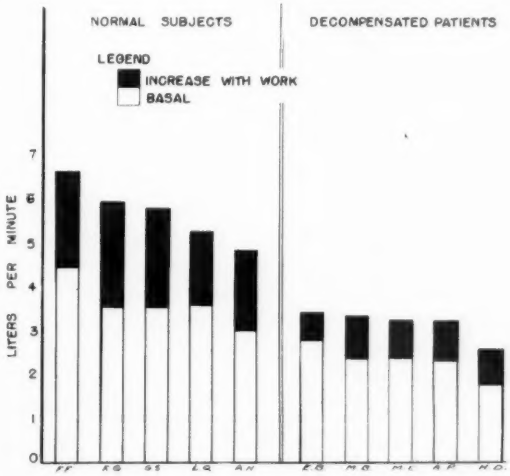

Chart 1.—Cardiac output at rest and after exercise.

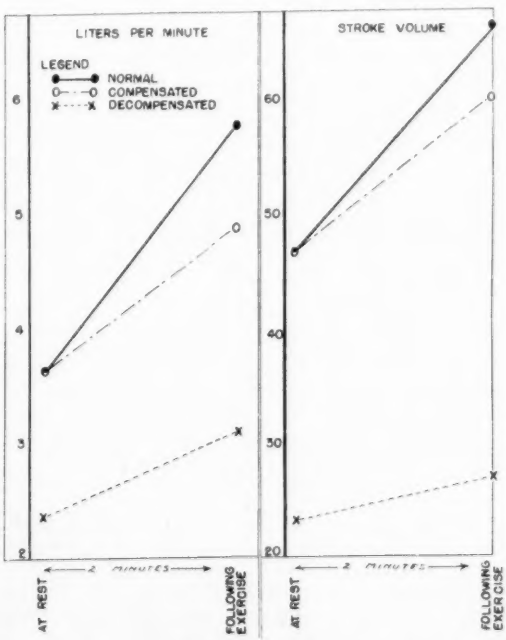

Chart 2.—Average cardiac output at rest and after exercise.

The average stroke volume of the normal subjects increased 19 cc. per beat after work; for the patients with compensated cardiac disease there was an average increase of 14 cc. per beat; for the patients with cardiac decompensation there was an average increase of only 4 cc. per beat.

No constant change in the arteriovenous oxygen difference following exercise occurred in any of the groups.

For the normal subjects the average increase in oxygen consumption with work was 148 cc. per minute; for the patients with compensated cardiac disease it was 111 cc. per minute, and for the patients with cardiac decompensation only 92 cc. per minute.

The pulse rate was accelerated moderately after exercise in the normal subjects and in the patients with decompensation.

However, we were surprised to find no acceleration of the pulse rate after exercise in 2 of the patients with compensated cardiac disease. Perhaps inadequate coronary blood flow may have been responsible. Failure of acceleration of the rate of the heart after exercise in patients with disease of the coronary arteries has been reported by Bierring, Larsen and Nielsen.[8]

We have made no extensive study of the influence of strenuous exercise on cardiac output. However, in 1 patient with congestive heart failure who was asked to exercise by lifting the dumb-bells until dyspnea forced him to discontinue the procedure, the cardiac output increased only 1.05 liters per minute. With similar exercise of three minutes' duration 1 of the normal subjects increased his cardiac output by 3.51 liters per minute—a difference of 250 per cent, indicating that strenuous exercise of this character did not cause the cardiac output of the patient with decompensation to increase in a normal manner.

COMMENT

Experimental evidence for the validity of the acetylene method of measuring the cardiac output after exercise in normal persons has been reported by Bansi and Groscurth.[9] Grollman likewise concluded that the method is accurate during exercise if the cardiac output is not increased to more than 10 liters per minute.[10] Comparative studies with the acetylene and the direct Fick method have shown close parallelism of results for patients with cardiac decompensation under

8. Bierring, E.; Larsen, K., and Nielsen, E.: Some Cases of Slow Pulse Associated with Electrocardiographic Changes in Cardiac Patients After Maximal Work on Krogh Ergometer, Am. Heart J. **11**:416, 1936.

9. Bansi, H. W., and Groscurth, G.: Die Bestimmung des zirkulatorischen Minutenvolumens mittels Acetylen nach Grollman in der Ruhe und bei Arbeitsversuchen, Ztschr. f. d. ges. exper. Med. **77**:631, 1931.

10. Grollman, A.: Personal communication to the authors.

basal conditions, although the absolute values tended to be lower when the acetylene method was used.[11] As the mild exercise employed in this study caused no marked increase in cardiac output (less than 10 liters) and because of the safeguards of the three sample acetylene method in detecting recirculation, we believe that the measurements of blood flow after exercise have yielded significant values, though we fully realize that the method used, like all indirect methods, is not accurate to the cubic centimeter.

SUMMARY

The influence of similar measured exercise on the cardiac output of 5 normal subjects, 4 patients with compensated cardiac disease and 5 patients with cardiac decompensation has been determined.

In the normal subjects a considerable increase in cardiac output with exercise occurred, the average increase being 2.07 liters per minute.

In the patients with compensated cardiac disease the increase in cardiac output was moderate, the average increase being 1.21 liters per minute.

In the patients with congestive heart failure the increase in cardiac output with exercise was small, the average increase being 0.75 liter per minute.

These data suggest that in patients with severe cardiac decompensation under the conditions of these experiments the cardiac output is not increased with effort to the same degree as it is in normal persons and that relative inability to increase the cardiac output may have an important bearing on the pathogenesis of congestive heart failure.

11. McGuire, J.; Shore, R.; Hauenstein, V., and Goldman, F.: Relation of Cardiac Output to Congestive Heart Failure, Arch. Int. Med. **63**:290 (Feb.) 1939.

DERMATOMYOSITIS WITH SCLERODERMA, CALCINOSIS AND RENAL ENDARTERITIS ASSOCIATED WITH FOCAL CORTICAL NECROSIS

REPORT OF A CASE IN WHICH THE CONDITION SIMULATED ADDISON'S DISEASE, WITH COMMENT ON METABOLIC AND PATHOLOGIC STUDIES

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The clinical similarity between Addison's disease and the syndrome recognized as dermatomyositis with scleroderma may be marked. Confusion regarding the differential diagnosis is likely and has been discussed by Osler,[1] Winfield,[2] Boardman,[3] Longcope,[4] Rowntree and Snell,[5] Brown and his associates,[6] Howard[7] and others. The coexistence of these two diseases must be extremely uncommon, and the contemporary

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From the Medical Clinic, the Laboratory of Pathology and the Laboratory of Bacteriology of the Massachusetts General Hospital, and from the Fatigue Laboratory, Harvard University.

1. Osler, W.: On Diffuse Scleroderma, with Special Reference to Diagnosis, and to the Use of the Thyroid-Gland Extract, J. Cutan. & Genito-Urin. Dis. **16**:127, 1898.

2. Winfield, J. M.: A Case of Scleroderma, J. Cutan. & Genito-Urin. Dis. **22**:586, 1904.

3. Boardman, W. P.: Scleroderma, with Special Reference to Its Etiology and Treatment, Arch. Dermat. & Syph. **19**:901 (June) 1929.

4. Longcope, W. T.: Hypoglycemia in Scleroderma: The Metabolism in Eight Cases with Reference to the Function of the Glands of Internal Secretion, J. A. M. A. **90**:1 (Jan. 7) 1928.

5. Rowntree, L. G., and Snell, A. M.: A Clinical Study of Addison's Disease, Philadelphia, W. B. Saunders Company, 1931.

6. Brown, G. E.; O'Leary, P. A., and Adson, A. W.: Diagnostic and Physiologic Studies in Certain Forms of Scleroderma, Ann. Int. Med. **4**:531, 1930.

7. Howard, C. P.: Scleroderma with Calcinosis, Canad. M. A. J. **37**:124, 1937.

literature contains few reliable reports. Lewin and Heller [8] in a review of 508 cases of scleroderma reported before 1895 noted that the dual diagnosis had been made in only 4. Osler [1] reviewed these cases and did not consider that any of the patients had Addison's disease. In 1908 Lichtwitz [9] reported a single case in which the two diseases coexisted clinically; the observation was confirmed at autopsy. Recently Leriche, Jung and De Bakey [10] reported the occurrence of Addison's disease in a patient under treatment for scleroderma. Autopsy was not performed, however, and the diagnosis can be accepted only with reservation.

In this communication we shall report clinical, metabolic and pathologic observations on a woman who was admitted to the hospital with a presumptive diagnosis of Addison's disease. Suspicion of adrenal insufficiency was based on a history of profound weakness and malaise, gastrointestinal disturbances, loss of weight and pigmentation of the skin. On physical examination there was postural hypotension. Laboratory studies showed a diminished concentration of total base and of sodium in the serum and an increased concentration of nonprotein nitrogen. A negative chloride balance and a positive potassium balance were observed while the patient was under a metabolic regimen. The patient improved in a satisfactory manner with a high salt intake and rest in bed. During this treatment, however, the skin became shiny, taut and atrophic, and the presence of dermatomyositis with scleroderma became apparent. Eleven months after the onset of symptoms and three months before death subcutaneous nodules were palpable, and roentgen examination revealed calcinosis. At postmortem examination the adrenal glands were normal in size and appearance. The significant anatomic diagnoses were chronic nonsuppurative dermatomyositis, scleroderma, calcinosis and obliterative endarteritis of the kidneys.

During the first period of hospitalization, while the patient was under observation in the metabolic ward, studies of the electrolyte balance were completed. One year later, a month before death, she was observed a second time in the same ward, and the studies were repeated. Observations of the acid-base balance of the blood were made at frequent intervals during the illness and on the day of death.

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8. Lewin, G., and Heller, J.: Die Sclerodermie: Eine monographische Studie, Berlin, A. Hirschwald, 1895.

9. Lichtwitz, L.: Ueber einem Fall von Sklerodermie und Morbus addisonii nebst Bemerkungen über die Physiologie und Pathologie des Sympathicus und der Nebennieren, Deutsches Arch. f. klin. Med. **94**:567, 1908.

10. Leriche, R.; Jung, A., and De Bakey, M.: The Surgical Treatment of Scleroderma, Surgery **1**:6, 1937.

REPORT OF CASE

H. T. W., a Canadian-born woman aged 26, a housewife, was admitted to a ward in the Massachusetts General Hospital on Dec. 7, 1935, with a tentative diagnosis of Addison's disease.

The family history revealed that the mother had died of tuberculous meningitis at the age of 46, eight years after she had been treated in a sanatorium for pulmonary tuberculosis. The patient had lived at home with her mother during this time.

The past history contained nothing of significance before the onset of the present illness. The patient had considered herself a strong, healthy girl and had been unusually free from minor illnesses. Before marriage she had worked in a box factory. No unusual occupational hazard was recognized during this employment.

The patient had been married for eighteen months. Four months prior to her admission to the hospital, after an uneventful pregnancy, she had given birth at full term to a normal child. During the antepartum period she had visited her family physician twice a month. At each visit the blood pressure was within the normal range. A trace of albumin was found in the urine on more than one examination. Because of this finding she was advised to restrict her salt intake during the last three months of pregnancy.

The present illness began about six weeks after delivery. She noted that her legs were weak and tired when she walked outdoors, although her strength seemed good while she was engaged in similar activity in the house. The weakness in the legs progressed, however, and she began to conserve her energy indoors as well. In climbing a flight of stairs she would often rest once or twice before she reached the top. Shortly after this she noticed some difficulty in extending her arms, and weakness, which had been confined to the legs, appeared in the upper extremities. There were no symptoms suggesting sensory or motor disturbance, and no fibrillary twitching of the muscles was noted.

One month before her admission to the hospital her friends observed a deep suntan-like pigmentation of the skin, although she had had no prolonged exposure to the sun for several months. Shortly after this, because of extreme weakness she was forced to give up all her household duties and would lie down or sit most of each day. Her appetite was good except on certain days, when she vomited recently ingested food. After her pregnancy she had menstruated normally three times. She had skipped one period immediately preceding entry. She had lost about 20 pounds (9.1 Kg.) in weight. Her family physician made a tentative diagnosis of pellagra because of the pigmentation. Dr. Albert H. Covner, of Lynn, Mass., was consulted and made a presumptive diagnosis of Addison's disease. He referred her to the Massachusetts General Hospital.

Physical examination showed a poorly nourished woman of slender stature. Patchy areas of pigmentation were superimposed on a skin, which seemed darker than usual for a blond. The deeply pigmented areas were principally around the breasts, in the axillary folds and on the abdomen and the buttocks. There was no increased pigmentation of the mucous membrane of the mouth. The elbows could be extended through an arc of only about 110 degrees and the knees through an arc of about 90 degrees. The skin about these joints was slightly taut. No other pathologic changes in or about the joints were noted. The blood pressure with the patient lying down was 120 systolic and 80 diastolic, and with the patient standing, 86 systolic and 70 diastolic.

Clinical Laboratory Data.—The specific gravity of the urine was 1.024. No sugar, albumin or blood cells were noted at either of two examinations. The red blood cell count was 4,870,000; the leukocyte count, 10,200. The differential count showed 63 per cent polymorphonuclears, 32 per cent lymphocytes, 4 per cent eosinophils and 1 per cent basophils. The Hinton reaction of the blood was negative. The basal metabolic rate at two determinations was + 18 and + 5 per cent, respectively. There was no free hydrochloric acid in the gastric contents one hour after injection of 0.5 mg. of histamine phosphate U. S. P. and ingestion of 50 cc. of 7 per cent alcohol.

The concentration of sodium in the serum was 127.3 milliequivalents per liter, the concentration of protein was 7.9 Gm. per hundred cubic centimeters and the concentration of nonprotein nitrogen was 52 mg. per hundred cubic centimeters.

Roentgen Examination.—The following interpretations were reported by Dr. J. R. Lingley: "Examination of the chest shows no evidence of disease. A flat plate of the abdomen and films of the renal region show no significant changes from the normal."

Course During First Period of Hospitalization.—A tentative diagnosis of Addison's disease and scleroderma was made, and the patient was transferred to the metabolic ward for further study. The electrolyte exchange with a metabolic regimen showed a negative chloride balance and retention of potassium. These observations appeared to confirm the diagnosis of adrenal insufficiency. The patient improved with a high intake of sodium chloride, and the concentration of sodium in the serum returned to normal.

Approximately one month later cutaneous atrophy in an early stage was noted, and the limitation of articular motion increased. At this time lumbar puncture was done, and because of unexpected findings this was repeated on three occasions. The initial pressure varied between 80 and 150 mm. of water. The fluid was always clear, and no clot was demonstrated. There were never more than 3 white blood cells per cubic millimeter. The concentration of total protein varied between 67 and 105 mg. per hundred cubic centimeters. The concentration of sugar varied between 63 and 67 mg. The colloidal gold curve at each determination was approximately 5555433210. The Wassermann reaction of the spinal fluid was negative.

A neurologic consultant made the following observations: "There is generalized muscular weakness of the voluntary muscles but no evidence of muscular atrophy, spasticity or flaccidity. There are no involuntary movements. All reflexes except the abdominal reflexes are present and normal."

A biopsy of the skin was reported by Dr. Charles S. Kubik as follows: "There are well marked degeneration and fibrosis of the corium, with extensive infiltration by lymphocytes, plasma cells and a small number of monocytes. The findings are similar to those observed in some cases of muscular weakness associated with arthritis and scleroderma."

The patient remained in the hospital more than three months. The rectal temperature fluctuated between 99 and 101 F. The daily fluctuations were intermittent at times and during two periods suggested a Pel-Ebstein type of fever. The pulse rate varied between 90 and 100 and the respiratory rate between 20 and 24. The postural hypotension persisted. The average blood pressure with the patient lying down was about 100 systolic and 70 diastolic and with the patient standing was about 90 systolic and 70 diastolic. During hospitalization she had remissions and relapses, but it was believed that the disease was becoming progressively worse when she was discharged, on March 7, 1936.

Interval History.—During the succeeding five months the patient became weaker and spent more and more time in bed. The limitation of motion of the elbows and knees increased, presently involving the lumbar and the dorsal portion of the spine. She was advised to continue to take 10 Gm. of sodium chloride in capsules each day but soon became discouraged and did this irregularly. In June 1936 she noted soreness of the mouth and tongue, associated with a failing appetite. Early in August she became so weak that she remained in bed continually. On advice she entered the hospital for further study on August 21.

Second Admission.—Physical examination showed the following changes which had developed since her discharge from the hospital. The skin was atrophic and shiny over most of the body. It was dry and scaly. The face was pinched, drawn and pale. There was limitation of motion in the joints of all extremities and of the lumbar and the dorsal portion of the spine. A few hard subcutaneous nodules were present in the right axillary fold. Elsewhere subcutaneous nodules were not felt, because of the tenseness of the skin. There appeared to be generalized atrophy of the facial, truncal and skeletal muscles. The temperature, the pulse rate and the respiratory rate were similar to those observed during the first period of hospitalization.

Laboratory Data.—The specific gravity of the urine was 1.029. No abnormal constituents were noted. The red blood cell count was 4,280,000; the leukocyte count, 9,000. The blood smear was normal. The basal metabolic rate at two examinations was + 3 and + 1 per cent, respectively. The colloidal gold curve was unchanged.

Roentgen Examination.—The following report was made: "There has been no change in the appearance of the chest since the previous examination. Roentgenograms of the shoulder show calcification in the soft tissues of the axillary folds. Examination of the elbows shows extensive linear calcification in the soft tissues on their medial aspects. The right hand shows an area of calcification between the thumb and the index finger. Both legs show calcification in the soft tissues on the lateral aspects of the fibula, and both feet show calcification between the first and the second metatarsal bone. There is no evidence of sclerodactylia."

Course During Second Period of Hospitalization.—The patient was transferred to the metabolic ward on October 29 and was observed for three five-day periods during which she was given a diet low in calcium, with 10 Gm. of sodium chloride added. One week before death the specific gravity of the urine failed to exceed 1.010, and the excretion of 0.6 mg. of phenolsulfonphthalein injected intramuscularly was 7 per cent in the first twenty-five minutes and 39 per cent after two hours and ten minutes. The patient continued to grow weaker, and she died on November 30.

Gross Postmortem Examination.—The skin of the entire body was thickened, taut and glossy. There was brown pigmentation, more pronounced in the natural folds of the skin. The interosseous muscles were atrophied, and the hands showed apelike configuration.

The subcutaneous fat was scanty and indurated. Within the panniculus and the connective tissue planes throughout the body there were numerous opaque, white, granular, calcium-like deposits, the largest of which were 2 cm. in diameter. The skeletal muscular tissue was universally thinned and atrophic and because of its pallor had the appearance of uncooked breast of chicken.

The serous coats exhibited normal color and unimpaired sheen. The peritoneal cavity contained 2,000 cc., each pleural cavity 250 cc. and the pericardium 340 cc. of relatively clear yellowish fluid.

The upper lobe of the left lung contained a few peripherally situated, partially circumscribed fibrosed nodules measuring up to 0.5 cm. in diameter. Except for moderate congestion and focal atelectasis the remainder of the pulmonary substance was normal.

No evidence of residual thymic tissue was observed within the mediastinum.

The heart weighed 240 Gm. The myocardium was pale but normal in consistency. The wall of the right ventricle measured 0.2 cm. in thickness, and the left, 1.2 cm.

The aorta and the large arteries contained a few scattered noncalcified, atheromatous plaques measuring up to 0.5 cm. The vascular walls were thin, but the elasticity was unimpaired.

The liver weighed 1,680 Gm. Its surface was pale reddish brown, it was smooth and its substance was firm but moderately friable. The lobules were pale, and the central veins were prominent and engorged.

The spleen weighed 150 Gm. The cut surface was firm and the removable pulp diminished. The follicles were unusually prominent.

The adrenal glands weighed together 20 Gm. They were of normal appearance.

The kidneys weighed together 200 Gm. The capsules stripped without difficulty and revealed yellowish red mottled surfaces. The surfaces were irregularly ridged and furrowed. The furrows measured less than 1 mm. in breadth, and the ridges, the surfaces of which were smooth, measured up to 5 mm. On section the cortex measured 4 to 6 mm. The areas subjacent to the surface depressions were paler than the remainder of the parenchyma. Although circumscribed, these pallid foci were not sharply demarcated and revealed no regular configuration. They did not extend throughout the entire depth of the cortex, and corticomedullary demarcation was normal.

All other organs, including the central nervous system, were examined and observed to be grossly normal.

Culture of blood from the heart at necropsy was sterile.

Microscopic Postmortem Examination.—Adrenals: Multiple sections showed no pathologic changes.

Skin: The epidermis was thinned, the rete pegs were flattened and broadened, and the basal layer contained an increased amount of brown granular pigment. The corium contained a few pigment-bearing phagocytes but no significant inflammatory exudate. Superficially the dermis manifested a thin layer with a fibrillar edematous appearance. In the deeper layers (fig. 1) the collagen was thickened and increased in amount, with diminution in the number of blood vessels and coil glands. Within the subcutaneous fat there were increased numbers of interlacing strands of fibrous tissue. Constituent collagen was focally swollen and poorly stained and exhibited granular fragmentation, with infiltration by hemosiderin-laden macrophages and abundant foam cells. Many foci of foam cells were present in otherwise unchanged fat, and there were also varying amounts of amorphous and granular eosinophilic substance as well as deeply basophilic spicules and blocks of calcified material. Calcification was accompanied by the presence of numerous monocytes and multinucleated foreign body giant cells and was most pronounced in the deeper portions of the panniculus overlying the diseased muscles.

Skeletal Muscle: The sections included pharyngeal, esophageal and diaphragmatic muscle as well as specimens from muscles of the extremities. The changes were spotty but widespread, and the lesions were variable. All areas manifested different phases, and some areas, all stages of severe myositis. There

was profound variability in the caliber of the muscular fasciculi, and many showed shrinkage, with wide separation from the perimysium. Occasionally the bundles were eosinophilic, swollen and lacking in striation. The majority, however, were frayed, and there was separation of the myofibrillae. Isolated muscular strands displayed marked nuclear proliferation; others were totally replaced by fibrous scar. There were scattered foci of lymphocytic infiltration (fig. 2) distributed perivascularly and also within the interstitial tissue. In some regions the lymphoid exudate actually replaced disintegrating muscle substance, and pseudofollicle forma-

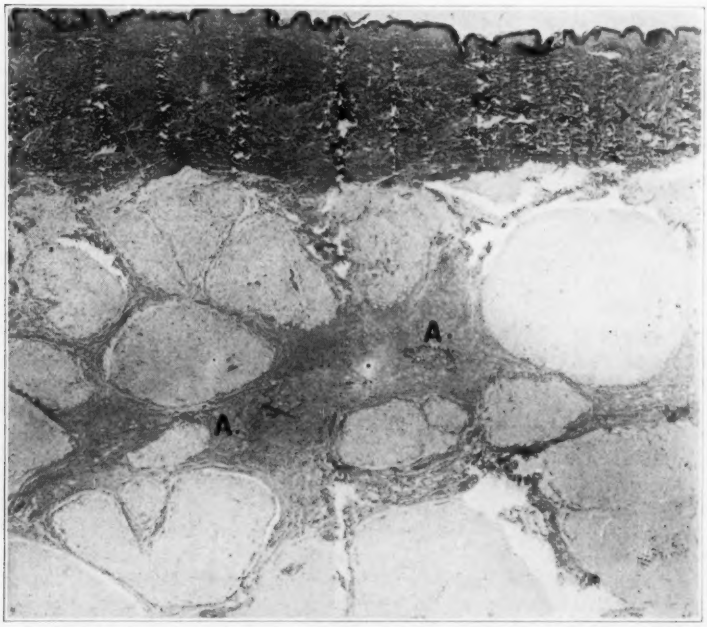

Fig. 1.—Skin, showing the narrow epidermis and dense, compact, relatively avascular dermis. The subcutaneous tissue exhibits interlacing fibrous strands and foci of calcification (*A*).

tion was observed. The noteworthy feature of the muscular changes was the extent as well as the degree of the involvement.

Peripheral Nerve: The sections examined showed no significant changes within the fibrillae. Irregularly distributed, however, in the perineural sheath were small aggregations of lymphocytes and plasma cells.

Kidney: The histologic appearance was, in our experience, unique. Examination of the cortex by means of low power magnification revealed an alteration of foci of relatively normal architecture, with narrow bands of atrophic tissue corresponding to the depressions noted in the gross examination. Glomeruli appeared to be evenly distributed through both the normal and the atrophic areas

(fig. 3), but in the latter the tubules were entirely different. Instead of the usual large, conspicuous convoluted tubules with narrow lumens clustered about the glomeruli, there were only small tubules lined with low cuboidal cells which stained intensely with dye for basophilic material. The appearance simulated that of malfunctioning fetal tubules, a phenomenon of regeneration previously noted by Kaufmann,[11] Maatz [12] and Mallory.[13] All evidence of brush border was lacking. The normal convoluted tubules were separated from each other by a rich capillary network and only a delicate reticulum. The abnormal tubules were embedded in abundant, fairly dense and relatively avascular fibrous stroma.

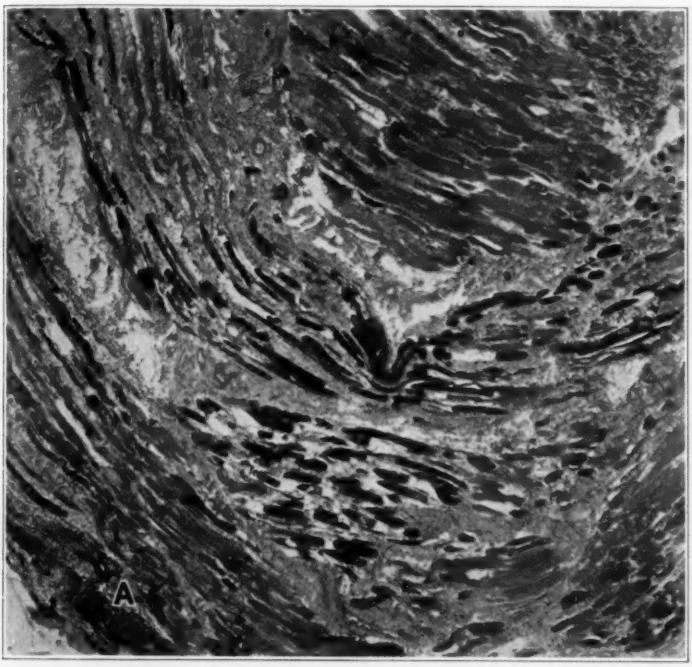

Fig. 2.—Skeletal muscle, showing variability of staining power, irregular replacement by fibrous tissue and focal aggregation of lymphocytes (*A*).

Careful inspection of the apparently normal areas showed that in them also there were focal areas of degeneration. Groups of convoluted tubules showed coagulation necrosis of the epithelium, loss of staining power of the nuclei and

11. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie für Studierende und Aerzte, Berlin, E. de Gruyter & Co., 1922, vol. 2, p. 109.

12. Maatz, R.: Experimentelle tubuläre Schrumpfniere durch vorübergehende Gefässabklemmung, Frankfurt. Ztschr. f. Path. **46**:438, 1934.

13. Arteriosclerosis, Generalized, Marked Aortic, Coronary and Renal. Cabot Case 23041, New England J. Med. **216**:170, 1937.

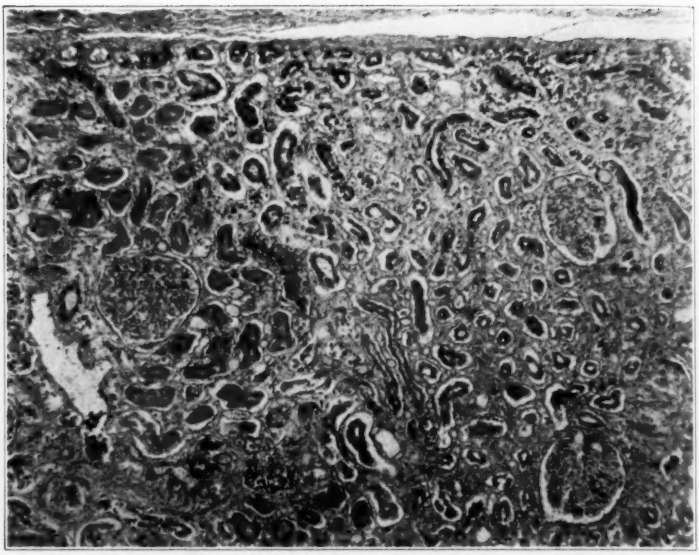

Fig. 3.—Adjacent areas in the renal cortex. The convoluted tubules on the left are of normal size but exhibit evidence of acute infarction. Those on the right show the fetal character and stromal increase described in the text. The glomeruli in both regions are normal.

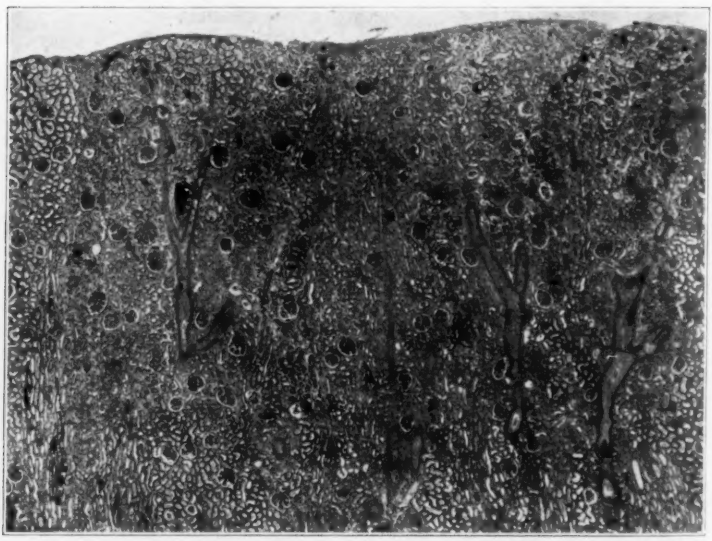

Fig. 4.—The uniform subendothelial thickening of the course of each interlobular artery is well shown. There is evident focal variation in the convoluted tubules, but the glomerular distribution is not affected.

occasional polymorphonuclear infiltration. The appearance was that of infarction, but there were two striking differences—the glomeruli within these acutely degenerating areas were normal, and there was little significant reaction in the stroma at their periphery, i. e., no hemorrhage or fibrosis and but scanty leukocytic infiltration.

The cortical damage was probably associated with the vascular lesions, which were limited to the interlobular arteries supplying the areas of degeneration. Medullary branches of the renal artery appeared to be normal, as were the arcuate

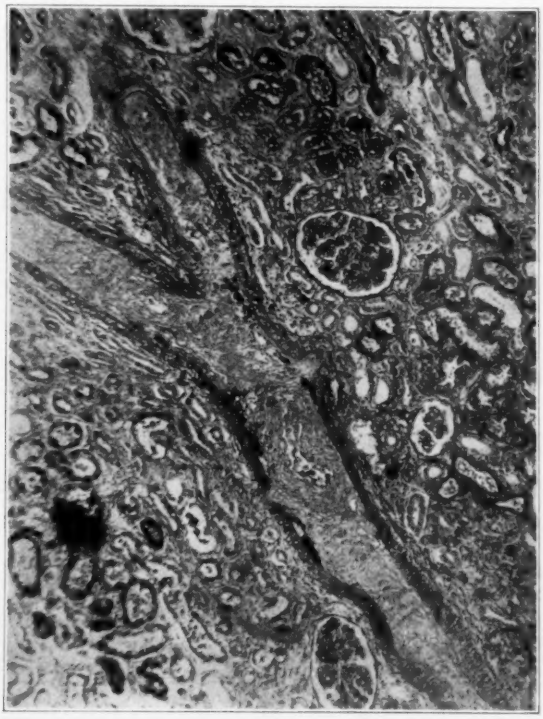

Fig. 5.—A higher power view of an interlobular artery in longitudinal section. The subendothelial proliferative process extends along its entire course into its major branches, and only a narrow segment of lumen is visible.

arteries, although the latter showed a peculiar intimal thickening in some segments. Radiating interlobular arteries, however, displayed an abrupt change at their points of origin except in regions where the process had begun within the arcuate artery.

Certain sections showed involvement of the entire course of a radiating artery (fig. 4) and its larger intralobular branches by a bizarre form of endarteritis. The subintimal substance was infiltrated by a sparsely nucleated, palely basophilic, mucinous material which had the appearance of Wharton's jelly. A few lesions

apparently of earlier origin exhibited frank subintimal fibrosis replacing the mucoid substance. Stains for elastic tissue showed limitation of the lesion to the intima, and in most areas the internal elastic lamina was intact. Several of the older fibrous lesions, however, exhibited reduplication of elastic tissue. Stains for fat showed granules of lipoid material within the mucoid substance in the intima. The endarteritic process extended into the larger intralobular arteries, but directly these vessels assumed the caliber of afferent arterioles the intimal changes ceased as abruptly as they had begun.

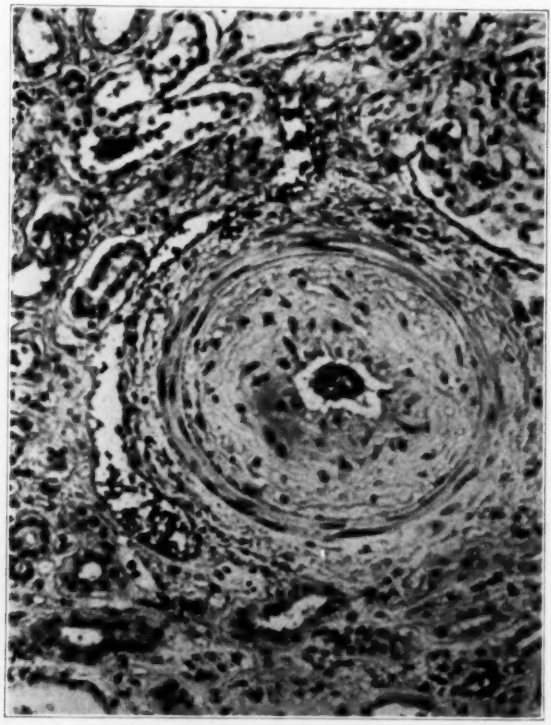

Fig. 6.—An interlobular artery in cross section. The muscularis is intact, but the mucinous subendothelial process and the narrowing of the lumen are noteworthy.

The lumens were markedly narrowed, often to slitlike orifices, as the result of intimal thickening (figs. 5 and 6). The lining endothelial cells were swollen and basophilic but displayed no actual proliferation. Occasional vessels were occluded by hemorrhagic thrombi, with fibrinoid necrosis which was limited to the intima and the inner half of the muscularis. Slight exudation was associated with this necrosis (fig. 7), but certain arteries, apparently those previously thrombosed, exhibited complete fibrous organization without recanalization.

Liver: Uniformly within the central half of all lobules the endothelial lining was widely separated from the underlying cell cords and exhibited fibrinoid thickening. The hepatic cells were shrunken, and immediately surrounding the central vein of each lobule there was a single layer of necrotic parenchymatous cells. The sinusoids contained large numbers of polymorphonuclear cells, although there were relatively few red blood cells. The peripheral half of the lobules exhibited marked and contrasting swelling, with coarse vacuolation in abundance.

Spleen: The splenic corpuscles were enlarged, and most of them possessed secondary nodules. Although the apparent germinal centers contained a few active-looking stem cells, the predominant cell was a mononuclear phagocyte which was frequently vacuolated. There was slight central fibrosis but no necrosis.

Lymph Nodes: The normal architecture was preserved, but the stroma and sinuses were filled with large numbers of mononuclear and multinuclear phagocytes.

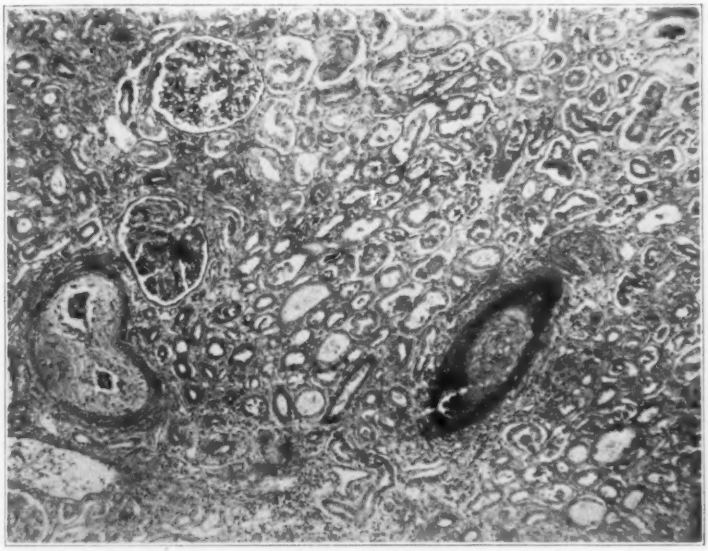

Fig. 7.—Two adjacent vessels with different lesions. The artery on the left shows the proliferative process without necrosis. The vessel on the right exhibits acute necrosis of the muscularis.

The follicles, as in the spleen, contained well formed central nodules of cells similar to those in the stroma and sinuses.

Lungs: The alveoli were normal. The nodules observed grossly showed interstitial fibrosis and varying degrees of infiltration with lymphoid cells, monocytes and a few polymorphonuclears. Many alveoli were compressed and lined with cuboidal epithelial-like cells. The pathogenesis of these changes was uncertain.

None of the other organs showed significant parenchymatous abnormalities. All the viscera, however, revealed a slight to moderate grade of vascular change. This consisted of slight subintimal fibrosis, with narrowing of the arterial lumens.

The muscle coats were thickened in places, and there was some perivascular fibrosis. The arterioles frequently showed hyaline intimal thickening. These histologic observations were most evident in the skeletal muscles, the ovaries, the myometrium, the spleen, the myocardium and the region of the fibrotic pulmonary nodules. Serial sections of the pituitary and the parathyroid glands were normal. The bones showed no evidence of active decalcification.

Anatomic Diagnosis.—The following diagnosis was made: chronic diffuse dermatomyositis with scleroderma, generalized interstitial calcinosis, focal renal tubular infarction, obliterating endarteritis of the interlobular renal arteries, generalized arteriosclerosis and arteriolosclerosis (slight), central lobular necrosis of the liver and follicular hyperplasia of the spleen and the lymph nodes.

Metabolic Studies.—On her first admission to the metabolic ward the patient was given a constant diet low in sodium for two five day periods. The first five days was used as a preliminary period to allow establishment of approximate nitrogen equilibrium, and no excreta were collected. The food was purchased for five days at a time, and one half of a duplicate day's diet from the second period was weighed, dried and analyzed. The methods employed for analysis of the blood, excreta and diets have been described.[14]

Harrop[15] has shown that when a patient with adrenal insufficiency is given a diet low in salt there may be a significant negative chloride balance. It has been observed in this laboratory[16] and reported by Wilder and his associates[17] that there may be simultaneous retention of potassium. During the five day period of observation of our patient there were a negative chloride balance (tables 1 and 2) of 15 milliequivalents per day and a positive potassium balance of a similar amount. Stool collections were not made during the first period of hospitalization. These data, therefore, do not include excretion of electrolytes in the feces.

During the second period in the hospital, one year later, the patient was given a diet low in calcium with added sodium chloride for three five day periods. A preliminary period was prescribed as before, and data from the second and the third period only are included in the tables. During these periods stool collections were made. This ten day period of study showed certain changes not previously observed. The chloride and the potassium imbalance were confirmed, but the amounts were considerably less than those initially noted. With a high sodium intake the negative balance of this constituent was 35 milliequivalents per day. The total excretion of calcium was about four times that contained in the diet and was about equally divided between the urine and the stool. The total excretion of phosphate was only 12 per cent greater than the intake.

Nitrogen equilibrium was not reached during the second period of observation; in fact, there was a positive balance of 21 per cent. Thus, in terms of nitrogen

14. Talbott, J. H.; Jacobson, B. M., and Oberg, S. A.: The Electrolyte Balance in Acute Gout, J. Clin. Investigation **14**:411, 1935. Dill, D. B.; Talbott, J. H., and Consolazio, W. V.: Blood as a Physiochemical System: XII. Man at High Altitudes, J. Biol. Chem. **118**:649, 1937.

15. Harrop, G. A., and Weinstein, A.: Studies on the Suprarenal Cortex: I. Cortical Suprarenal Insufficiency and the Action of the Cortical Hormone upon the Normal and Suprarenalectomized Dogs, J. Exper. Med. **57**:305, 1933.

16. Talbott, J. H.: Unpublished data.

17. Wilder, R. M.; Kendall, E. C.; Snell, A. M.; Kepler, E. J.; Rynearson, E. H., and Adams, M.: Intake of Potassium, an Important Consideration in Addison's Disease: A Metabolic Study, Arch. Int. Med. **59**:367 (March) 1937.

exchange the patient was not suffering from a wasting disease. The concentration of ammonia in the urine was included because it is believed to be an index of renal function. In the presence of severe renal damage, formation or excretion of ammonia by the kidneys may be diminished.[18] There is no evidence from the data on this patient that this function of the kidneys was seriously impaired up to a few weeks before death.

The experimental observations on arterial blood for the year during which the patient was under observation are given in table 3. The cell volume was normal when it was first observed but gradually diminished as death approached. When the oxygen capacity was determined it was below normal but was pro-

TABLE 1.—*Fluid Intake and Urinalysis*

		Urine								
Date December 1935	Total Fluid Intake, Cc.	Volume, Cc.	Total Fixed Base, mEq.	Sodium, mEq.	Potassium, mEq.	Calcium, mEq.	Ammonia, mEq.	Chloride, mEq.	Phosphate, Mg.	Total Nitrogen, Gm.
14-15.....	2,230	1,805	.....	91.7	58.1	5.0	.....	95.7	524	6.73
15-16.....	1,910	1,175	.....	61.3	56.1	5.3	.....	72.7	484	6.92
16-17.....	2,030	1,520	.....	79.5	61.0	5.2	.....	87.4	531	6.86
17-18.....	2,030	1,165	.....	54.4	45.7	4.6	.....	61.4	531	6.75
18-19.....	2,030	1,430	.....	63.9	54.0	5.3	.....	67.5	566	6.82
November 1936										
3- 4.....	2,680	1,970	261.9	225.7	25.4	8.5	20.3	219.0	185	4.71
4- 5.....	2,680	1,600	230.0	201.8	19.8	8.3	24.1	201.0	204	4.35
5- 6.....	2,680	1,630	239.5	204.5	19.3	8.0	22.9	201.0	269	4.14
6- 7.....	2,680	2,350	325.5	284.8	26.6	9.8	34.1	270.8	329	4.75
7- 8.....	2,680	1,530	204.3	171.5	21.6	7.5	24.6	177.0	237	4.16
8- 9.....	2,680	1,700	275.2	233.0	21.3	6.6	25.0	221.0	260	3.88
9-10.....	2,680	1,870	239.0	206.0	23.0	6.9	39.8	195.5	262	3.98
10-11.....	2,680	1,200	200.0	174.4	20.0	6.3	46.7	172.5	236	4.20
11-12.....	2,680	1,790	249.6	225.5	24.9	7.0	62.6	221.5	261	4.44
12-13.....	2,680	720	106.5	90.4	13.0	4.0	24.3	90.7	173	2.88

TABLE 2.—*Summary of Metabolic Data*

	First Admission, 5 Day Period			Second Admission, 10 Day Period			
	Intake	Urinary Excretion	Daily Balance*	Intake	Urinary Excretion	Fecal Excretion	Daily Balance
Sodium, mEq.	386	351	+ 7.0	1,823	2,018	173	—35.3
Potassium, mEq.	353	275	+15.6	361	215	93	+ 5.3
Calcium, mEq.	240	25	+43.0	33	73	96	—14.6
Chloride, mEq.	308	385	—15.6	1,947	1,970	48	— 7.1
Phosphate, mg.	2,400	2,640	—48.0	3,980	2,420	2,190	—63.0
Total nitrogen, Gm.....	....	....	.....	62	42	7	+ 1.3

* Balance for intake and urinary output only.

portional to the decrease in cell volume. The concentration of sugar in the blood was normal on five determinations.

The acid-base balance of the serum was extremely interesting. On none of the days when it was observed was it normal. The concentration of sodium in the serum on entry was 127.3 milliequivalents per liter; this increased after institution of a diet rich in salt to 138.4 milliequivalents per liter. During the next six months it remained slightly below normal, and after that it decreased progressively as the patient became lax in taking added salt. On September 21 the

18. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 1.

concentration was 126.8 milliequivalents per liter, the lowest value observed. The patient was again given a high salt diet, and again the concentration of sodium increased. On the day of death it was 137.4 milliequivalents per liter. The concentration of chloride in the serum, on the other hand, was either normal or slightly below normal, and on none of the days when it was observed was it less than 97.4 milliequivalents per liter. In the classic form of Addison's disease [19] the decrease in the chloride content of the serum is quantitatively similar to the decrease in sodium. Although this sequence of events is not invariable, the failure of our patient to conform should have suggested that the chemical changes were not primarily the result of adrenal insufficiency. The concentration of potassium was determined in two specimens of serum and found to be normal.

The concentration of calcium was normal on two determinations and slightly below normal on a third. The concentration of phosphate on two determinations was normal. The concentration of serum protein, on the other hand, was 7.7 Gm.

TABLE 3.—*Experimental Observations on Arterial Blood and Plasma*

	Whole Blood			True Plasma								
Date	Oxygen Capacity, Vol. %	Cell Volume, %	Sugar, Mg. per 100 Cc.	Total Base, mEq. per Liter	Sodium, mEq. per Liter	Potassium, mEq. per Liter	Calcium, mEq. per Liter	Bicarbonate, mEq. per Liter	Chloride, mEq. per Liter	Phosphate, mEq. per Liter	Protein, Gm. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.
12/11/1935.....	...	39.5	98	....	127.3	..	..	...	105.7	..	7.7	52
12/17/1935.....	...	39.4	97	....	132.5	..	..	26.2	104.1	..	7.3	36
12/30/1935.....	...	38.0	96	....	138.4	..	..	25.1	102.1	..	7.5	40
1/14/1936.....	...	40.7	111	.....	137.1	..	..	23.6	101.6	..	7.9	24
2/21/1936.....	...	39.9	103	....	136.4	..	..	25.2	98.9	..	..	34
4/ 3/1936.....	15.1	36.5	...	146.7	136.8	..	..	25.8	102.6	..	8.4	34
6/12/1936.....	15.1	37.3	...	....	133.8	..	..	23.5	98.4	..	9.3	20
9/21/1936.....	14.0	32.1	...	139.2	126.8	..	..	25.4	101.3	..	9.0	..
10/14/1936.....	13.8	31.1	...	137.9	128.5	..	..	25.0	97.4	..	8.2	20
10/27/1936.....	...	32.4	...	139.4	130.7	3.9	4.0	26.4	97.9	2.1	8.3	20
11/13/1936.....	...	31.8	...	143.3	132.3	..	5.0	24.2	103.6	2.2	8.3	20
11/30/1936.....	...	...	...	148.1	137.4	4.8	4.4	...	100.3	..	8.4	34

per hundred cubic centimeters on admission, and during the eight months before death it was more than 8.1 Gm. The maximum concentration observed was 9.3 Gm.

Complete data for acid-base balance were not obtained for each specimen of blood. In several samples taken during the last three months of life, however, the sum of the acids was greater than the total base content. Thus, on October 27 the sum of the acids was 146.5 milliequivalents per liter, and the total base content was 139.4 milliequivalents per liter. Two explanations for these unusual observations may be offered. Calculation of base bound by protein, according to Van Slyke and others,[20] may not be applicable to the serum in this case. This

19. Loeb, R. F.: Chemical Changes in the Blood in Addison's Disease, Science **76**:1932, 1932.

20. Van Slyke, D. D.; Hastings, A. B.; Hiller, A., and Sendroy, J., Jr.: Studies of Gas and Electrolyte Equilibria in Blood: XIV. The Amounts of Alkali Bound by Serum Albumin and Globulin, J. Biol. Chem. **79**:769, 1928.

is in agreement with the reports by Gutman and Gutman,[21] who have observed in some serums with an increased concentration of globulin the inapplicability of the formula. Secondly, an increase of the total acid over the total base content is not a unique observation [22] and would possibly be noted in other diseases if this relation were investigated.

The nonprotein nitrogen content of the serum was 52 mg. per hundred cubic centimeters on entry and decreased to 24 mg. in the following eight weeks. During the second period of hospitalization the concentration of this constituent remained below 22 mg. per hundred cubic centimeters until the day of death, when it was 35 mg.

The Wassermann reaction of the blood and spinal fluid as well as the Wassermann reaction of the husband's blood was negative. The colloidal gold curves were probably associated with the increased concentration of globulin in the serum and spinal fluid and were not thought to be indicative of syphilis of the central nervous system.

COMMENT

It is believed that a presumptive diagnosis of Addison's disease as well as scleroderma was justified on this patient's admission to the hospital, as most of the criteria were satisfied. There were a history of exposure to tuberculosis, symptoms of weakness and malaise, gastrointestinal disturbances and considerable loss in weight. On physical examination the pigmentation of the skin was typical of the patchy pigmentation seen in certain patients with chronic adrenal insufficiency. Postural hypotension was demonstrated. The concentration of sodium in the serum was 127.3 milliequivalents per liter on entry and increased to 138.4 milliequivalents per liter when a high salt regimen was instituted. The nonprotein nitrogen content was above normal initially and decreased during treatment. A negative chloride balance was observed when the patient was studied in the metabolic ward. The diagnosis of Addison's disease seemed inaccurate, however, as the scleroderma progressed and calcinosis developed. In retrospect, we believe that for a diagnosis of Addison's disease the only important criterion lacking was pigmentation of the mucous membranes. The possibility of partial adrenal insufficiency during the first period of hospitalization, as in the case recorded by MacCallum,[23] appeared to be excluded by the absence of autopsy evidence of previous damage to the glands. MacCallum's patient suffered from acute scleroderma and at autopsy showed adrenal atrophy.

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21. Gutman, A. B., and Gutman, E. B.: Relation of Serum Calcium to Serum Albumin and Globulin, J. Clin. Investigation **16**:903, 1937.

22. Gutman, A. B.; Gutman, E. B.; Jillson, R., and Williams, R. D.: Acid-Base Equilibria of the Blood in Diseases Associated with Hyperglobulinemia, with Special Reference to Lymphogranuloma Inguinale and Multiple Myeloma, J. Clin. Investigation **15**:475, 1936.

23. MacCallum, W. G.: Acute Diffuse Scleroderma, Tr. A. Am. Physicians **41**:190, 1926.

It is frequently difficult clinically to differentiate scleroderma and dermatomyositis, and in consideration of the observations at autopsy such a differentiation is believed to be futile in this instance. Raynaud's disease and sclerodactylia may precede or be associated with scleroderma. This patient had neither the acute symptoms of the first condition nor the localized decalcification characteristic of the second. Generalized decalcification of the skeleton was seen at roentgen examination, but this was not confirmed by the histologic studies.

The possibility that this disturbance might be related to a primary disorder of calcium and phosphorus metabolism, such as calcinosis universalis,[24] cannot be excluded. The concentrations of these constituents in the serum were normal at two examinations, however, and at the first entry a normal amount of calcium was excreted in the urine. During the second period in the hospital there was a moderate negative balance. Thyroid dyscrasia has been implicated in the pathogenesis of scleroderma by many observers.[25] There was no histologic or metabolic evidence of myxedema in this case, however, and determination of the basal metabolic rate showed no evidence of hyperthyroidism.

We shall discuss the anatomic observations with respect to (1) changes related to the muscular dyscrasia and (2) the changes in the kidneys. The distribution and variability of the histologic changes in the muscle were consistent with a diagnosis of idiopathic nonsuppurative myositis or dermatomyositis.[26] It seems probable that the abnormalities in the adjoining vessels were secondary to the surrounding inflammatory reaction. The perineural lymphocytic infiltration evidently had a similar pathogenesis. There was no histologic evidence to incriminate the central or the peripheral nervous system as a causative factor. Microorganisms such as have been described by Boothby[27] as present in the muscles of patients with myasthenia gravis were not demonstrated.

The inflammatory and reparative processes in the subcutaneous and the deeper connective tissue planes are also believed to be the result of

24. Bauer, W.: Calcinosis, in The Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1938, vol. 13. Bauer, W.; Marble, A., and Bennett, G. A.: Further Studies in Calcification of Subcutaneous Tissue ("Calcinosis Universalis") in a Child, Am. J. M. Sc. **182**:237, 1931.

25. Durham, R. H.: Scleroderma and Calcinosis, Arch. Int. Med. **42**:467 (Oct.) 1928. Castle, W. F.: The Endocrine Causation of Scleroderma, Including Morphea, Brit. J. Dermat. **35**:255, 1923.

26. (*a*) Langmead, F. S.: The Relationship Between Certain Rare Diseases: Generalized Scleroderma, Calcinosis, Dermatomyositis, and Myositis Fibrosa, Arch. Pediat. **40**:112, 1923. (*b*) Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925; vol. 1, p. 147. (*c*) Karlmark, E.: Zur Pathologie der Polymyositis, Acta med. Scandinav. **72**:59, 1929.

27. Boothby, W. M.: Myasthenia Gravis, Tr. A. Am. Physicians **51**:188, 1936.

adjacent muscular destruction.[28] It is recognized that calcification frequently follows inflammation and degeneration of adipose tissue.[29] With so diffuse an inflammatory background as this, widespread calcinosis may be an anticipated sequela. Similarly, the scleroderma may possibly be attributed to an extension of the underlying inflammatory process and its effect on the vascular and nervous supply of the skin.[30] The relation of the resultant dermatomyositis to true scleroderma is uncertain,[31] but the overlapping of the histopathologic changes associated with these conditions suggests a common cause for both.[26a]

If it is granted that the dermatomyositis has an inflammatory pathogenesis, any attempt to correlate the condition with the degenerative lesion in the kidneys is relatively unsuccessful. The lack of similarity between the vascular changes in the muscles and the bizarre arterial lesions in the kidneys is obvious. It is possible that the vascular lesions in the kidneys were the result of mild but continuous irritation. Substances liberated by muscular degeneration, in combination with the disordered cutaneous excretory power, may have been the source of this irritation. Scriver and Oertel[32] have recorded observations which suggest a specific susceptibility of the renal interlobular arteries to noxious stimuli. They have reported acute bilateral necrosis of the renal cortex in occasional cases of late toxemia of pregnancy. There is little evidence to suggest that our patient had severe toxemia of pregnancy, although her physician found albumin in the urine before delivery and her symptoms began six weeks post partum. In kidneys with bilateral cortical necrosis the lesions are generally acute and in the same stage of development.[33] Nevertheless, the distribution of the process is similar to that observed in this patient, and the kidneys grossly resembled those described in the literature.[34]

28. Klingman, W. O.: Dermatoneuromyositis Resulting in Scleroderma, Arch. Neurol. & Psychiat. **24**:1187 (Dec.) 1930.

29. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 493.

30. Rake, G.: On the Pathology and Pathogenesis of Scleroderma, Bull. Johns Hopkins Hosp. **48**:212, 1931.

31. Klingman.[28] Wells.[29]

32. Scriver, W. de M., and Oertel, H.: Necrotic Sequestration of the Kidneys in Pregnancy (Symmetrical Cortical Necrosis): A Clinical and Anatomic-Pathologenetic Study, J. Path. & Bact. **33**:1071, 1930.

33. De Navasquez, S.: The Histology and Pathogenesis of Bilateral Cortical Necrosis of the Kidney in Pregnancy, J. Path. & Bact. **41**:385, 1935.

34. (*a*) Jardine, R., and Teacher, J. H.: Two Cases of Symmetrical Necrosis of the Cortex of the Kidneys Associated with Puerperal Eclampsia and Suppression of Urine, J. Path. & Bact. **15**:137, 1911. (*b*) Bamforth, J.: A Case of Symmetrical Cortical Necrosis of the Kidneys Occurring in an Adult Man, ibid. **26**:41, 1923. (*c*) Bradford, J. R., and Lawrence, T. W. P.: Endarteritis of the Renal Arteries Causing Necrosis of the Entire Cortex of Both Kidneys, ibid. **5**:195, 1898.

In view of the macroscopic resemblance it is of interest that in both conditions the vascular lesions are limited to the interlobular arteries. Although intimal thickening is not regularly observed in cases of acute necrosis, several cases reported in the literature,[35] as well as an unreported case from this hospital have included evidence of chronic fibrous thickening of the intima in addition to hyaline thrombosis. It is believed that in this case, only the massive thrombosis accompanying puerperal cortical necrosis is lacking to complete the histologic picture.

The arterial lesion in this case was unusual in other respects. It was confined to the intima, it involved uniformly the postarcuate and the prearteriolar segments of the renal arterial tree and it had an unusual mesenchymal appearance (fig. 6). The last mentioned phenomenon has been termed mucoid endarteritis by Jores[36] and is probably an early manifestation of a subintimal process terminating in fibrosis. Medial changes were limited to those vessels in which thrombosis occurred. In these areas partial necrosis was present, but the involvement rarely extended beyond the central portion of the muscular coat. Even in the absence of an occlusive process (figs. 4 to 6) the arterial lumens were sufficiently stenosed to produce ischemia.

The selective tubular degeneration was associated with the diminution in vascular supply, and the foci of actual cortical necrosis occurred only in areas where the thrombosis had occluded the nutrient vessels. MacCallum[37] has shown that each cortical artery terminates in a glomerular tuft from which an efferent arteriole transmits blood to a plexus surrounding a convoluted tubule. A descending medullary vessel reforms from this plexus and in turn joins an anastomotic network in the medullary substance. If this is so it is possible that the glomeruli suffer less from the ischemia than the other elements of the nephron. Relative glomerular resistance to oxygen lack has been demonstrated by Fahr,[38] Maatz[12] and Zeckwer.[39] It is believed that the absence of significant changes in the collecting tubules may be related to the rich capillary anastomoses in the medulla.

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35. Jardine and Teacher.[34a] Bradford and Lawrence.[34c]

36. Jores, L.: Arterien: Produktive Endarteritis, in Henke, F., and Lubarsch, O.: Handbuch speziellen pathologischen Anatomie und Histologie, Berlin, 1924, Julius Springer, vol. 2, p. 644.

37. MacCallum, D. B.: The Arterial Blood Supply of the Mammalian Kidney, Am. J. Anat. **38**:153, 1926.

38. Fahr, T.: Kreislaufstörungen in der Niere, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6, pt. 1, p. 148.

39. Zeckwer, I. T.: The Persistence of the Glomerular Circulation Following Occlusion of the Renal Vein of One Kidney in the Cat, Am. J. Path. **2**:57, 1926.

The renal process may therefore be interpreted as incomplete bilateral cortical necrosis similar in many respects to that reported by Branson [40] and by Mallory.[18]

It is not believed, however, that the patient died of renal insufficiency. It is a fact that three weeks before death the ability to concentrate solids was lost and that excretion of phenolsulfonphthalein was below normal. Opposed to these two clinical tests are the following points: (1) lack of elevation of the concentration of nonprotein nitrogen or of phosphate in the serum, (2) lack of evidence of acidosis as determined by the concentration of serum bicarbonate, (3) lack of diminution of ammonia excretion and (4) adequate excretion of fluid and salts. Nor is there evidence that this patient was suffering from chronic nephritis of long duration, which has been known to lead to "metastatic" calcification with hyperplasia of the parathyroids.

Both Maatz [12] and MacNider [41] have shown that renal tubules severely injured by ischemia or by noxious substances may regenerate with undifferentiated epithelium. MacNider has shown that the functional effectiveness of such epithelium is appreciably impaired. Since it is recognized that the convoluted tubules are intimately associated with salt exchange,[42] it is possible that the negative salt balance in our case was caused by these morphologic changes.[43]

The degenerative changes noted in the liver and lymphoid follicles must have resulted from relatively severe systemic toxemia. If these changes are considered in conjunction with the muscular and renal lesions a common pathogenic agent may be assumed. Furthermore, diffuse vascular lesions such as the patient showed are not infrequently encountered in elderly persons and in persons with hypertension. This patient, however, was only 26 years of age and had no elevation of blood pressure. The arterial changes, though individually insignificant, when viewed as a whole link themselves with the other focal processes and assume greater importance as a manifestation of a systematic disease the precipitating cause of which remains obscure.

SUMMARY

Studies of a patient with dermatomyositis, scleroderma and calcinosis are reported. On entry the clinical diagnosis was Addison's

40. Branson, W. P. S.: Obliterative Arteritis, Tr. Path. Soc. London **56:** 212, 1905.

41. MacNider, W. de B.: A Study of Renal Function and the Associated Disturbance in the Acid-Base Equilibrium of the Blood in Certain Experimental and Naturally Acquired Nephropathies, Arch. Int. Med. **26:**1 (July) 1920.

42. Smith, H. W.: The Physiology of the Kidney, New York, Oxford University Press, 1937.

43. Pohl, J.: Ueber subakute Nephritis, Arch. f. exper. Path. u. Pharmakol. **67:**233, 1911.

disease. This was apparently substantiated by a history of weakness, gastrointestinal disturbances, loss of weight and cutaneous pigmentation. On physical examination there was postural hypotension. Metabolic studies showed a negative sodium and a negative chloride balance. In the blood there was an increased concentration of serum protein, a decreased concentration of total bases and an excess of determined acid over determined base. With a high intake of sodium chloride there was a transient regression of symptoms.

At necropsy the adrenal glands were normal. There was severe dermatomyositis associated with deposition of calcium in the connective tissue planes. A peculiar form of mucoid endarteritis limited to the interlobular arteries of the kidneys was associated with ischemic changes in the renal cortex. The similarity of these changes to those observed in bilateral renal cortical necrosis of pregnancy was noted. The initiating factor of the visceral and diffuse muscular lesions was not evident.

NOTE.—Since the submission of this paper for publication a report [44] has appeared of a case of scleroderma with generalized visceral and cutaneous vascular changes. Although the arterial lesions in the two cases exhibited a degree of similarity, there was considerable difference in the distribution, variation and apparent severity of the process. Myositis, calcinosis and focal renal infarction were not recorded. Moreover, necropsy revealed extensive glandular tuberculosis with terminal miliary spread. There were also Aschoff nodules in the myocardium. Metabolic studies were not performed.

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44. Masugi, M., and Yã, S.: Die diffuse Sklerodermie und ihre Gefässveränderung, Virchows Arch. f. path. Anat. **302**:39, 1938.

RELATION OF HYPERTHYROIDISM TO HYPERTENSION

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Since hyperthyroidism is a general disease in which one of the most fundamental physiologic processes of the body is abnormally accelerated, it influences organic functions generally. The changes in vascular tonus and the increase in cardiac output and in velocity of blood flow are usually reflected in some alterations of blood pressure. In the characteristic case, the systolic pressure shows a slight to moderate elevation while the diastolic pressure remains relatively unchanged or is slightly lowered, resulting in an increase of pulse pressure. That these changes represent physiologic responses to the disease is indicated by the fact that the pressures assume their previous normal levels with remission of the metabolic rate to a normal basal level.

There are, however, cases in which the systolic pressure is higher than that occurring in the kind of case just indicated or in which both the systolic and the diastolic pressure are considerably elevated. In these cases the pressures either are uninfluenced by remission of the hyperthyroidism or fail to return completely to normal levels with this remission. To investigate such cases, the following analyses were compiled. From these records it is possible to distinguish two types of cases, which will be discussed subsequently.

ANALYSES OF CASES

The data which follow were obtained from 265 cases of hyperthyroidism. The patients were 211 women and 54 men, and all were treated by subtotal thyroidectomy. For the entire group the average age was 36 years, the duration of toxic symptoms thirteen months and the basal metabolic rate + 43.4 per cent. The preoperative blood pressure averaged 140 mm. of mercury systolic and 76.5 diastolic. The systolic pressure exceeded 150 mm. in 80 cases, or 30 per cent of the series, 160 mm. in 50, or 18.9 per cent, and 200 mm. in 9, or 3.4 per cent. These observations are shown in greater detail in table 1. This table also shows that in general the patients with higher pressure were older and had had thyrotoxic symptoms for a longer time.

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Assuming that a systolic pressure above 145 mm. of mercury is definitely abnormal, I attempted to make follow-up observations in all cases in which the systolic pressure was above this level and the postoperative period exceeded twelve months. Records were obtained in 38, or approximately one half, of the cases, and a comparison of the preoperative and postoperative blood pressure levels is shown in tables 2 and 3.

The 38 cases have been divided into two groups: (1) those in which the preoperative systolic pressure was between 145 and 170 mm. of mercury, and (2) those in which it was 170 mm. or more.

In the first group there were 26 cases. In 19, or 73 per cent, of these the systolic pressure one year or more after operation showed some reduction from the preoperative level, and in 14 of the 19, or

TABLE 1.—*Data Obtained from Analyses of Two Hundred and Sixty-Five Cases of Hyperthyroidism*

			Averages					
Classification	Number of Patients	Percentage of Total Cases	Systolic Pressure	Diastolic Pressure	Pulse Pressure	Basal Metabolic Rate, %	Age of Patient	Duration of Toxic Symptoms, Mo.
Total cases studied.....	265	....	140	76.5	63	+43.4	36	13
Systolic pressure over 150..	80	30	...	....	....	.....	....	..
Systolic pressure over 160..	50	18.9	177	90	90.5	+43.5	41.5	20
Diastolic pressure over 90..	50	18.9	...	....	....	.....	....	..
Systolic and diastolic pressure over 150/90.....	37	14	...	....	....	.....	....	..
Systolic and diastolic pressure over 160/100.....	14	5.2	193	110.7	....	+38	45.5	28.5
Systolic pressure over 200..	9	3.4	226	103	110	+37	45.5	25

53 per cent, of the group there was considerable reduction; in 9 cases the pressure became normal. There was a reduction of diastolic pressure in 12 cases. Systolic pressure increased in 4 cases and diastolic pressure in 9 cases. There was no change of pressure in 2 cases.

In the second group there were 12 cases (table 3). In 5 of these, or 45.4 per cent, reductions of both the systolic and the diastolic pressure had followed thyroidectomy and had been maintained for periods of one to five years. In 3 of the 5 cases the pressure was nearly normal. In 3 cases there was an increase of pressure, in 2 of them an extreme increase. In 2 cases there was little or no change of pressure.

Combining the figures from the two groups shows that in 19 cases the blood pressure was uninfluenced by relief of hyperthyroidism and either remained unchanged or continued to increase. In 19, or an equal number of cases, however, the blood pressure was appreciably reduced after thyroidectomy, and in 11 it became relatively normal or nearly normal.

TABLE 2.—*Analysis of 26 Cases of Hyperthyroidism in Which the Patient Had a Preoperative Systolic Pressure Between 145 and 170*

Age	Sex	Duration of Toxic Symptoms	Basal Metabolic Rate, %	Pathologic Condition	Preoperative Pressure		Pressure 1 Year or More After Operation		Reduction, Mm.		Increase, Mm.	
					Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
45	F	1 yr.	+37	Adenomatous hyperplasia...	160	72	132	68	28	4	..	..
18	F	1 yr.	+55	Hyperplasia.....	155	100	119	83	36	17	..	..
39	F	4 mo.	+34	Carcinoma.....	160	100	122	78	38	22	..	..
56	F	2 mo.	+49	Adenomatous hyperplasia...	166	66	150	90	16	..	..	24
32	F	3 yr.	+46	Adenomatous hyperplasia...	160	106	115	70	45	36	..	..
35	F	4 yr.	+75	Hyperplasia.....	150	95	130	70	20	25	..	..
18	F	6 mo.	+18	Hyperplasia.....	165	90	124	72	41	18	..	..
22	F	4 yr.	+59	Adenomatous hyperplasia...	160	80	140	80	20	0	..	..
46	F	3 mo.	+28	Adenomatous hyperplasia...	160	90	168	100	..	..	8	10
38	F	4 yr.	+23	Adenoma.....	168	110	182	120	..	..	14	20
21	F	10 mo.	+68	Hyperplasia.....	150	80	140	90	10	..	..	10
37	F	2 yr.	+17	.....	145	100	180	100	..	..	35	0
62	F	5 mo.	+91	Hyperplasia.....	150	70	150	68	..	..	..	..
46	F	3 yr.	+23	Hyperplasia.....	150	90	126	82	24	8	..	..
45	F	.....	+41	Hyperplasia.....	155	80	126	80	29	0	..	..
49	F	5 yr.	+94	Hyperplasia.....	156	70	170	90	..	..	14	20
33	M	2 mo.	+36	Hyperplasia.....	150	70	146	82	4	..	..	12
57	F	1 yr.	+33	Adenomatous hyperplasia...	158	78	140	100	18	..	..	22
24	F	3 yr.	+37	Adenomatous hyperplasia...	155	72	132	86	23	..	..	14
47	M	6 mo.	+54	Hyperplasia.....	150	90	140	75	10	15	..	..
35	F	2 yr.	+43	Hyperplasia.....	145	94	130	80	14	14	..	..
22	F	2 yr.	+52	Hyperplasia.....	152	82	125	70	27	12	..	..
34	F	3 yr.	+26	Adenomatous hyperplasia...	155	75	155	94	..	..	0	19
30	F	3 mo.	+54	Hyperplasia.....	150	80	120	73	30	7	..	..
56	M	3 yr.	+29	Adenomatous hyperplasia...	150	80	150	80	0	0	..	..
25	M	4 yr.	+46	Hyperplasia.....	150	90	128	84	22	6	..	..

TABLE 3.—*Analysis of 12 Cases of Hyperthyroidism with Hypertension in Which the Patient Had a Systolic Pressure of 170 or More*

Age	Sex	Duration of Toxic Symptoms	Basal Metabolic Rate, %	Pathologic Condition	Preoperative Pressure		Pressure 1 Year or More After Operation		Reduction, Mm.		Increase, Mm.	
					Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
62	F	2 yr.	+28	Adenomatous hyperplasia...	250	120	180	80	70	40	..	..
32	F	7 yr.	+78	Hyperplasia.....	200	100	120	72	80	28	..	..
47	F	18 mo.	+43	Cystic adenoma.....	182	100	142	80	40	20	..	..
25*	F	1 yr.	+63	Hyperplasia.....	178	80	65	50	113	30	..	..
41	F	1 yr.	+31	Adenomatous hyperplasia...	172	90	230	124	..	..	58	34
48	F	1 yr.	+75	Hyperplasia.....	170	90	164	90	6	0	..	..
26	F	6 mo.	+25	Hyperplasia.....	170	90	130	85	40	5	..	..
48	F	2 yr.	+51	Adenomatous hyperplasia...	170	90	210	100	..	..	40	10
56	M	2 yr.	+55	Adenomatous hyperplasia...	170	90	180	90	..	..	10	0
58	M	2 yr.	+48	Adenomatous hyperplasia...	180	110	130	90	50	20	..	..
23	M	6 mo.	+51	Hyperplasia.....	170	80	170	88	..	..	0	8
48	F	9½ mo.	+60	Adenomatous hyperplasia...	230	140	210	140	20	0	..	..

* Since this patient also had diabetes mellitus and Simmond's disease her case was not included in the statistical calculations.

COMMENT

As stated previously and as indicated by the data compiled in tables 2 and 3, cases of hyperthyroidism with hypertension which exceeds that considered physiologic can be classified as of two types:

1. A type in which hyperthyroidism and an established hypertension coexist incidentally in the same person as separate, unrelated entities. Usually the hypertension is essential in type, although its severity apparently is increased by the thyrotoxic state, and some improvement may follow release from hyperthyroidism. Despite symptomatic improvement, however, the blood pressure, both systolic and diastolic, remains high and usually is not significantly lowered, and the disease continues to progress.

2. A type in which relief of hyperthyroidism by subtotal thyroidectomy causes both the systolic and the diastolic pressure to recede promptly to a much lower, normal or nearly normal level, at which it remains or from which after a period of many months it again gradually ascends. This response suggests that thyrotoxicosis in these cases either is directly responsible for the hypertension or, more likely, precipitates or exaggerates a latent vascular disorder. It is conceivable that an inelastic or restricted vascular bed, capable of receiving the normal cardiac output without appreciable elevation of blood pressure, would be unable to receive the increased output incident to hyperthyroidism without a sharp rise in the propelling force. Conversely, with lessening of the output by remission of hyperthyroidism the pressure required to propel the blood is diminished. In other words, this hypothesis assumes the existence of arteriolar pathologic changes which are insufficient to increase appreciably the resistance to a normal volume of blood flow but which are sufficient to prevent normal expansion as the load is increased.

This hypothesis finds support in the observations which follow. In 5 cases (3 of the group in table 3 and 2 private cases not included in the present series) determinations were made of the response of blood pressure to exercise and to the cold pressor test of Hines and Brown.[1] These determinations are shown in table 4. In all cases large reductions of blood pressure had developed and been sustained after subtotal thyroidectomy.

After the basal level of blood pressure had been obtained, each patient was given sufficient exercise to increase the pulse rate appreciably (from 16 to 40 beats per minute), and the blood pressure was determined immediately afterward and at subsequent intervals of sixty

1. Hines, E. A., and Brown, G. E.: The Hereditary Factor in the Reaction of Blood Pressure to a Standard Stimulus (Cold), Proc. Staff Meet., Mayo Clin. **10**:371 (May 29) 1935.

seconds. In each instance the pressure rose to the approximate preoperative resting level. Moreover, these levels were sustained abnormally long and receded abnormally slowly. Thus the response of blood pressure to the increased cardiac output incident to exercise was approximately the same as that recorded preoperatively during the thyrotoxic state.

Each patient was then subjected to the cold pressor test described by Hines and Brown. In accordance with their technic the lowest or basal level of blood pressure was obtained with the subject resting supine for thirty minutes or longer. With the blood pressure cuff in place on one arm, the opposite hand was immersed in ice water (4 C.) to a point just above the wrist for sixty seconds, and readings of blood pressure were made thirty and sixty seconds after the beginning of immersion. Within thirty seconds the pressure again mounted to

TABLE 4.—*Effect of Exercise and of the Cold Pressor Test on the Blood Pressure of Patients Who Had Undergone Subtotal Thyroidectomy*

Case	Age of Patient	Preoperative Basal Metabolic Rate	Postoperative Pulse Rate (Resting)	Blood Pressure				Pulse Rate	
				Preoperative	Postoperative	After Exercise	After Immersion of Hand	After Exercise	After Immersion of Hand
1	47	43	76	182/100	142/ 80	195/ 95	185/105	104	82
2	58	48	84	180/110	130/ 90	190/100	185/105	110	92
3	62	28	68	250/120	180/ 80	230/110	230/110	100	74
4	60	62	82	210/110	150/105	220/112	218/110	98	80
5	56	58	72	190/115	150/108	190/120	200/124	112	72

approximately the same level which followed exercise. In the light of the studies of Hines and Brown, the reaction of the blood pressure in these patients was excessive and abnormal, as is that in all subjects afflicted with essential hypertension. The studies of these investigators showed that in addition to the persons with hypertension there is a group of persons who do not have hypertension but do give excessive reactions to the cold pressor test. Persons in this group they designated "hyperreacting normals," and they stated the belief that this excessive reaction indicates a latent quality and a likelihood of subsequent development of hypertension. On this basis it may be reasoned that my patients had potential if not real essential hypertension and that the latent factor had been precipitated or exaggerated by thyrotoxicosis.

It is interesting that in each of these 5 cases there was a familial history of hypertension.

CONCLUSIONS

1. As a physiologic response to hyperthyroidism, the systolic blood pressure is usually slightly or moderately elevated. It recedes to the normal level with relief of hyperthyroidism.

2. In a series of 265 cases which I studied, hyperthyroidism was associated with true essential hypertension in approximately 8 per cent and with elevations of the systolic pressure above the physiologic level (above 150 mm. of mercury) in 30 per cent. On the basis of changes of blood pressure following relief of hyperthyroidism, two types of cases are discernible: (1) cases with fixed or established essential hypertension, in which the blood pressure and the course of the vascular disease are not significantly influenced by relief of hyperthyroidism, and (2) cases with latent or labile essential hypertension, in which the blood pressure shows considerable reduction after relief of hyperthyroidism or approaches a normal level and maintains this level for a long period. In some cases of the second type the pressure is observed subsequently to ascend. In these cases there is excessive response in blood pressure to exercise and to the cold pressor test of Hines and Brown. It is suggested that the relation of hyperthyroidism to hypertension in these cases is provocative, that hyperthyroidism merely precipitates or exaggerates hypertension which is latent.

It is further suggested that in both types there is arteriolar disease, differing only in degree. In the first type the disease is more advanced, rendering the vascular bed inadequate for even a normal volume of blood flow. In the second type the disease may be designated as pretensive hypertension, which progresses to the condition of the first type with the advance of time.

CHRONIC CONSTRICTIVE PERICARDITIS

DYNAMICS OF THE CIRCULATION AND RESULTS OF SURGICAL TREATMENT

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Chronic constrictive pericarditis has received increasing attention in this country in the last ten years. White,[1] in 1935, brought together an excellent historic résumé of Pick's syndrome,[2] analyzed the clinical manifestations and recorded the experience which he and Churchill had had with surgical treatment—pericardiectomy. This treatment has been pursued most extensively in this country by Churchill and White,[3] Beck,[4] Blalock and Burwell [5] and us. The syndrome does not appear to be as uncommon as was formerly thought to be the case. The recognition of chronic constrictive pericarditis is important, since it is a cardiac lesion which lends itself to surgical treatment. We have observed 9 patients in the last two and one-half years. Since one group of workers do not have the opportunity to see large numbers of these patients in a short time, we are recording our investigations of the circulation in the

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An abstract of these studies was read before the Association of American Physicians, Atlantic City, N. J., May 5, 1937.

Drs. John E. Deitrick, Norman F. Crane, Robert F. Watson and Charles H. Wheeler assisted in the studies of the circulation.

From the Department of Medicine and the Department of Surgery of the New York Hospital and Cornell University Medical College.

1. White, P. D.: Chronic Constrictive Pericarditis (Pick's Disease), Treated by Pericardial Resection, Lancet **2**:539 and 597, 1935.

2. Pick, F.: Ueber chronische, unter dem Bilde der Lebercirrhose verlaufende Pericarditis (pericarditische Pseudolebercirrhose), nebst Bemerkungen über die Zuckergussleber (Curschmann), Ztschr. f. klin. Med. **29**:385, 1896.

3. Churchill, E. D.: Pericardial Resection in Chronic Constrictive Pericarditis, Ann. Surg. **104**:516, 1936. White.[1]

4. Beck, C. S., and Griswold, R. A.: Pericardiectomy in the Treatment of the Pick Syndrome: Experimental and Clinical Observations, Arch. Surg. **21**: 1064 (Dec., pt. 2) 1930. Beck, C. S., and Cushing, E. H.: Circulatory Stasis of Intrapericardial Origin: The Clinical and Surgical Aspects of the Pick Syndrome, J. A. M. A. **102**:1543 (May 12) 1934.

5. Burwell, C. S., and Flickinger, D.: Obstructing Pericarditis: Effect of Resection of the Pericardium on the Circulation of a Patient with Concretio Cordis, Arch. Int. Med. **56**:250 (Aug.) 1935.

presence of this syndrome together with our experience with the surgical treatment of 7 patients.[6] Clinical observations and studies of the circulation have been made in 9 cases. Resection of part of the pericardium was instituted in 7 of these cases and observations were made both before and after operation.

PLAN OF OBSERVATIONS

The patient was admitted to the hospital and remained in bed. The dietary intake of salt was limited to 2 Gm. daily and the fluid intake to 1,200 cc. A diet high in protein was given.

Measurements of the circulation were made shortly after the patient was admitted to the hospital, before diuretics were given. By means of medical treatment and drugs, the mobilization of fluids was then encouraged. When the patient had attained his best state, measurements of the circulation were repeated; then pericardial resection was done. At a time during convalescence when the patient was able to cooperate, observations were repeated and as frequently thereafter as changes in the clinical state were apparent. The patient was free from excess fluid on discharge to the outpatient clinic, from which he was readmitted to the hospital for repetition of the studies.

All observations were made in the morning while the patient was in a basal metabolic state. The cardiac output was estimated by the acetylene method, three samples of gas being taken, as first recommended by Grollman[7] and as further elaborated by Grollman, Friedman, Clark and Harrison.[8] During this measurement the patient sat in a steamer chair (at an angle of 135 degrees), having been trained beforehand to carry out the procedures. While he was at rest, the cardiac rate was counted at intervals of five minutes for one-half hour; at the end of this time the mixture of acetylene, air and oxygen was rebreathed. Three samples of gas were taken during each period of rebreathing for estimation of the arteriovenous oxygen difference. The first sample was obtained after the patient had taken ten to twelve breaths in twenty seconds, the second after two to three more breaths and the third after two to three additional breaths. All three samples were usually obtained before the end of thirty seconds. Samples were taken during expiration. Two or three periods of rebreathing were carried out at each measurement. Shortly afterward the oxygen consumption was measured with a Benedict-Roth spirometer. The vital capacity was measured, and the height and weight were recorded. An electrocardiogram was taken, the arm to tongue circulation time recorded, the venous pressure estimated and the blood pressure measured. Finally a roentgenogram of the heart was made at a distance of 2 meters. Sufficient time was allowed between each procedure for restoration of the basal metabolic state.

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6. Pericardial resection was carried out in these cases by one of us (Dr. Heuer).

7. Grollman A.: The Cardiac Output of Man in Health and Disease. Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 73.

8. Grollman, A.; Friedman, B.; Clark, G., and Harrison, T. R.: Studies of Congestive Heart Failure: XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, J. Clin. Investigation **12**:751, 1933.

The arm to tongue circulation time was estimated by the use of decholin, the patient lying quietly in the supine position.[9]

The venous pressure was measured by the direct method,[10] a large antecubital vein being used and the arm being placed on a level with the right auricle. Normal pressures recorded with this apparatus range from 4 to 10 cm. of saline solution. The antecubital vein of one arm was reserved for the injection of decholin and that of the other arm for the measurement of venous pressure. In subsequent measurements the vein was entered at the site first punctured.

Roentgenograms of the heart were taken during full inspiration, at a distance of 2 meters,[11] with the patient standing. Measurements of the cardiac area were carried out by the technic of Levy,[12] and estimations of volume were made as recommended by Bardeen.[13] Special exposures, anteroposterior as well as lateral, were taken for the detection of calcification. Examination under the fluoroscope was also carried out. Infra-red photographs were taken to record the state of the peripheral veins. The patient assumed as nearly as possible exactly the same position for each observation.

RESULTS OF STUDIES OF CIRCULATION

In all but 1 case (case 6) the measurements of the circulation followed a similar pattern.

Before operation the arteriovenous oxygen difference was increased (range, 71.5 to 88.6 cc.), the cardiac output per minute decreased, the cardiac index [14] decreased (range, 1.35 to 1.84 liters), the stroke volume decreased (range, 20 to 42 cc.), the venous pressure elevated (range, 17.9 to 24 cm.) and the circulation time prolonged (range, fifteen and four-tenths to twenty-nine and eight-tenths seconds) (table 1 and figs. 1 to 5).

After operation all the measurements approached or attained normal levels; in short, the arteriovenous oxygen difference approached or became normal (range, 51.4 to 68.7 cc.), the cardiac output per minute

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9. Tarr, L.; Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, Am. Heart J. **8**:766, 1933. Stewart, H. J.; Crane, N. F., and Deitrick, J. E.: Studies of the Circulation in Pernicious Anemia, J. Clin. Investigation **16**:431, 1937.

10. Taylor, F. A.; Thomas, A. B., and Schleiter, H. G.: A Direct Method for the Estimation of Venous Pressure. Proc. Soc. Exper. Biol. & Med. **27**:867, 1930.

11. The members of the Roentgenographic Department of the New York Hospital cooperated in this investigation.

12. Levy, R. L.: The Size of the Heart in Pneumonia: A Teleroentgenographic Study, with Observations on the Effect of Digitalis Therapy, Arch. Int. Med. **32**:359 (Sept.) 1923.

13. Bardeen, C. R.: Determination of the Size of the Heart by Means of X-Rays, Am. J. Anat. **23**:423, 1918.

14. The cardiac index represents the cardiac output in liters per square meter of body surface per minute.

increased, the cardiac index increased (range, 1.8 to 2.72 liters), the stroke volume increased (range, 33 to 50 cc.), the venous pressure fell (range, 8.3 to 16.7 cm.) and the circulation time became shorter (range, seven and three-tenths to seventeen and one-tenth seconds) (table 1 and figs. 1 to 5).

In certain cases the heart rate was elevated before operation and became slower afterward, and in others the reverse happened.

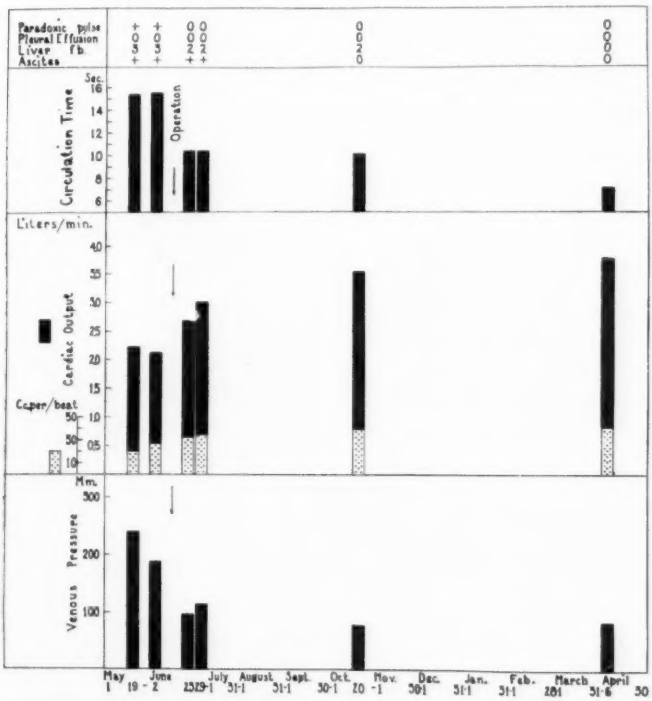

Fig. 1.—In this figure are plotted data relating to the cardiac output, venous pressure, circulation time and clinical signs in case 1, before and after pericardial resection. In this chart and some of the following charts *fb* indicates fingerbreadths and *Umb*, to the umbilicus.

The basal metabolic rate was not altered significantly from normal in the presence of this syndrome, nor did pericardiectomy change it.

The serum protein value was low in 2 cases (cases 5 and 6) and in the normal range in the others.

The vital capacity before operation was in the normal range unless there was pleural effusion. In certain cases it increased after operation;

in others the decrease was probably to be accounted for by the flexibility of the thoracic cage occasioned by removal of the ribs.

Preoperative infra-red photographs revealed an increase in the number, caliber and distention of the superficial veins. After operation the

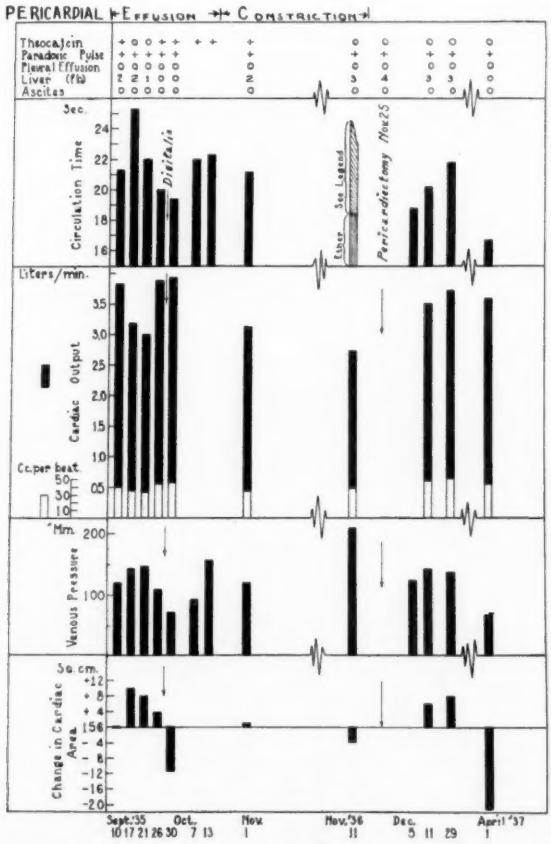

Fig. 2.—In this figure are plotted data relating to case 2. Because the patient was sensitive to decholin at this time it could not be used. "Ether time" is shorter than "decholin time," since the former is the arm to lung time and the latter the arm to tongue time.

veins became less conspicuous, and many channels became invisible (figs. 6 to 9).

Distention of the veins of the eyegrounds was marked before operation and decreased with the fall in venous pressure after operation.

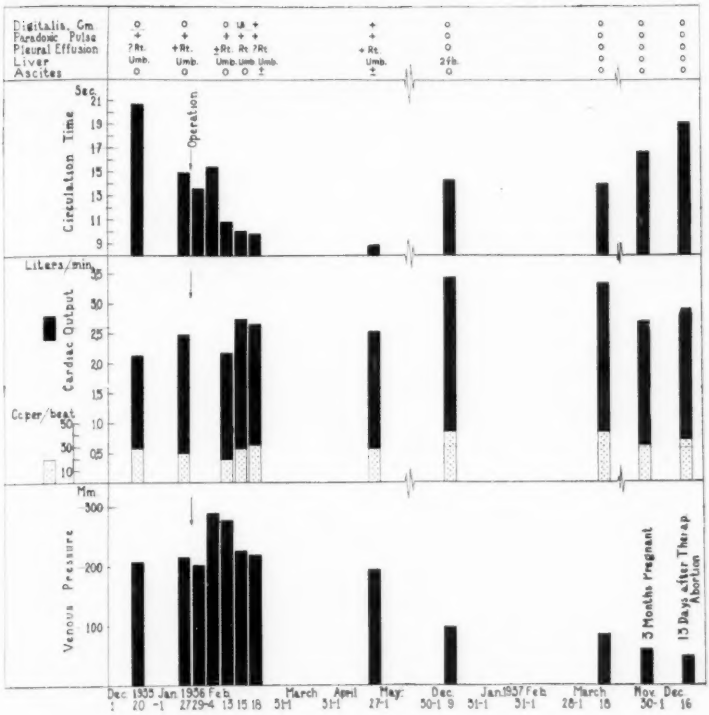

Fig. 3.—In this figure are plotted data relating to case 3.

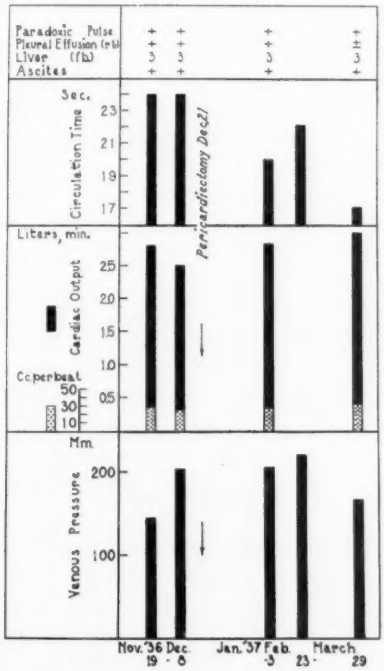

Fig. 4.—In this figure are plotted data relating to case 4.

TABLE 1.—*Data Relating to Nine Patients Suffering from Chronic*

Case, Age, Sex	Date	Weight, Kg.	Arterio-venous Oxygen Difference, Cc.	Cardiac Output, L. per Min.	Cardiac Output, L. per Sq. M. per Min.	Stroke Volume, Cc.	Arterial Pressure, Mm. Hg	Cardiac Area, Sq. Cm.	Left Ventricular Work, Gm. M. per Beat	Circulation Time, Sec.	Venous Pressure, Cm.	Vital Capacity, Cc.
1	5/19/36	40.9	71.7	2.23	1.70	20	93/84	82.2	24.2	15.4	24.0	1,900
15 yr.	6/ 2/36	37.0	66.5	2.12	1.70	27	82/70	79.9	27.9	15.5	18.8	1,850
F	6/ 5/36	(operation)										
	6/ 8/36	....	....	....	....	..	.....	....	....	....	17.5	
	6/23/36	34.7	52.1	2.67	2.20	32	85/60	86.4	31.8	10.4	9.6	1,350
	6/29/36	34.7	48.5	3.00	2.42	34	86/55	90.7	37.3	10.4	11.4	1,700
	10/20/36	39.7	43.3	3.53	2.70	39	90/68	93.3	41.9	10.1	7.8	1,800
	4/ 6/37	44.9	51.1	3.78	2.72	41	100/60	113.5	44.6	7.3	8.3	1,400
2	9/10/35	56.7	51.9	3.83	2.28	40	104/70	156.0	47.3	21.3	12.0	3,200
36 yr.	9/17/35	58.2	62.5	3.18	1.87	36	94/64	166.2	38.7	25.3	14.3	3,100
M	9/21/35	58.7	66.6	3.00	1.72	34	94/60	164.2	35.6	22.0	14.8	2,900
	9/26/35	58.0	53.9	3.88	2.28	45	98/68	159.8	50.8	20.0	11.0	3,500
	9/29/35	....	....	....	....	..						
	9/30/35	57.2	54.5	3.93	2.38	47	102/64	144.4	53.1	19.4	7.3	3,800
	10/ 7/35	....	....	....	....	..	.....	....	....	22.0	9.3	.....
	10/13/35	....	....	....	....	..	.....	.....	....	22.3	15.7	.....
	11/ 1/35	60.3	71.0	3.13	1.82	36	96/68	157.0	40.1	21.2	12.2	3,200
	11/11/36	59.5	74.2	2.74	1.60	39	115/90	152.1	54.6	18.4 (ether)	21.0	1,800
	11/25/36	(operation)								18.8	12.5	(Not basal)
	12/ 5/36	....	....	....	....	..	.....	.....	....	20.2	14.3	1,800
	12/11/36	54.7	56.3	3.51	2.14	49	95/68	162.1	54.6	21.8	13.8	2,500
	12/29/36	57.2	53.4	3.73	2.25	52	105/78	164.1	65.1	16.7	7.1	1,200
	4/ 1/37	53.8	53.8	3.59	2.19	45	95/75	134.6	52.0	19.2	9.2	.....
	1/28/38	....	....	....	....	..	.....	.....	....			
3	12/20/35	42.7	88.6	2.14	1.55	20	92/66	.....	31.1	20.7	20.8	1,500
30 yr.	1/27/36	45.9	81.2	2.48	1.76	25	92/70	.....	27.5	15.0	21.5	1,500
F	1/28/36	(operation)								13.7	20.3	
	1/29/36	....	....	....	....	..	.....	.....	....	15.5	29.0	.....
	2/ 4/36	....	....	....	....	..	110/82	.....	....	10.9	27.8	1,000
	2/13/36	47.7	85.0	2.19	1.52	20	100/75	.....	24.0			
	2/14/36	....	....	....	....	..						
	2/15/36	46.8	66.7	2.76	1.94	29	96/64	.....	32.0	10.2	22.7	900
	2/18/36	47.5	73.5	2.65	1.84	32	105/75	.....	39.0	9.9	22.0	950
	4/27/36	48.4	71.8	2.54	1.70	29	108/72	.....	35.5	9.0	19.3	1,400
	12/ 9/36	49.9	57.2	3.44	2.34	43	105/75	120.3	52.6	14.4	9.8	2,000
	3/18/37	51.5	54.9	3.35	2.25	42	80/50	119.0	37.0	14.0	8.5	2,600
	11/30/37	50.3	70.3	2.70	1.84	31	100/60	106.5	33.7	17.6	6.0	2,800
	12/16/37	49.7	62.4	2.90	2.00	36	90/65	104.4	38.2	12.4	4.8	2,850
4	11/19/36	61.3	81.2	2.81	1.63	29	98/70	165.5	33.1	24.0	14.5	1,400
20 yr.	12/ 8/36	61.5	81.7	2.51	1.44	26	100/70	155.6	30.0	24.0	20.4	1,400
M	12/21/36	(operation)										
	2/ 3/37	61.4	76.6	2.84	1.57	28	105/80	172.5	35.8	20.0	20.5	1,300
	2/23/37	....	....	....	....	..	.....	.....	....	22.1	22.0	.....
	3/29/37	59.4	68.7	3.01	1.80	33	90/70	170.9	35.9	17.1	16.7	2,000
	1/29/38§	65.1	....	....	....	..	110/80	163.7	....	21.5	18.8	1,700
5	8/21/36	64.0	83.1	2.22	1.35	34	122-116/78	141.1	45.8	18.6	17.9	1,650
44 yr.	9/22/36	57.0	71.5	2.69	1.71	34	128/72	129.4	46.2	18.4	13.8	2,250
F	9/28/36	(operation)										
	11/12/36	....	....	....	....	..	.....	.....	....	13.3	16.1	.....
	12/10/36	43.9	61.8	2.78	2.01	43	110/70	135.5	52.6	11.2	11.3	1,300
	3/31/37	57.7	75.3	2.78	1.76	35	128/68	.....	46.8	16.7	19.8	1,400
	2/ 1/38	58.1	64.2	3.16	2.02	38	100/80	.....	56.5	19.2	15.3	750
6	5/26/37	104.3	59.7	4.66	2.20	42	130/75	124.8	58.8	12.5	20.1	2,000
38 yr.	6/15/37	93.2	58.3	4.31	2.16	40	118/70	130.3	62.6	13.5	12.7	2,800
F	6/17/37	(operation)								10.2	11.1	1,900
	7/ 1/37	88.0	....	....	....	..	110/88	.....	....	9.0	10.2	
	8/ 6/37	....	....	....	....	..	.....	.....	....	16.7	12.9	3,350
	8/27/37	72.0	61.0	3.67	2.05	47	95/65	147.1	51.1	18.0	10.7	3,450
	11/19/37	72.4	65.5	3.39	1.88	46	120/80	142.4	62.6	19.5	8.7	3,600
	11/26/37	73.8	....	....	....	..	85/68	.....	....			
7	1/28/38	86.9	56.5	3.89	2.00	50	105/75	150.3	61.2	21.4	8.3	2,900
58 yr.	1/19/38	80.9	72.8	3.16	1.62	61	135/95	183.9	95.4	29.8	22.3	3,200
M	2/ 5/38	74.6	73.8	3.35	1.84	54	150/98	162.4	91.1	25.9	7.3	4,100
	4/12/38	84.6	....	....	....	..	160-145/100	.....	....	35.5	25.9	.....
	4/26/38	(operation)										
	6/13/38	74.0	76.8	3.00	1.59	48	142/90	194.8	75.7	28.9	16.4	2,800
8	6/ 1/35	70.6	81.9	2.99	1.00	34	104-94/68	165.1	38.4	22.8	18.2	4,600
29 yr.												
M												
9	12/11/34	49.7	74.7	2.69	1.82	32	128/70	99.5	43.1	10.6	14.5	1,600
13 yr.												
M												

* In all except cases 5 and 7 the[re] was normal sinus rhythm. The serum protein values were repeatedly shown to lie within normal limits in all except cases 5 and 6, in which the total protein value repeatedly remained between 4 and 5 Gm. On the days when special studies of the circulation were made, maintenance doses of digitalis or doses of other drugs were not given until after the studies had been completed.

† 0 indicates absent; +, present; ±, doubtful or questionable; ↑, increased; ↓, decreased.

Drugs, Gm.	Evidence of Congestive Heart Failure†								Red Blood Cells, Millions per Cu. Mm.	Hemoglobin, %‡	Comment
	Dyspnea	Cyanosis	Rales	Enlargement of Liver	Ascites	Edema	Pleural Effusion	Paradoxic Pulse§			
.....	0	0	0	+	+	0	0	+	3.8	76	Mercupurin (a mercurin-theophylline preparation) (1 cc.) was given intravenously on May 17, 1936
Aminophylline, 0.3	0	0	0	+	+	0	0	+	4.3	80	
0	0	0	0	+↑	+↑	0	0	0	4.8	80	
0	0	0	±	+	+	0	0	0			
0	0	0	±	+	0	0	0	±	4.1	92	
0	0	0	0	0	0	0	0	±	4.9	100	
Theocalcin, 4.5	+	+	0	+	0	0	0	+	5.8	112	No theocalcin was given between September 10 and 17; no theocalcin was given between November 6 and 11
0	0	+	0	0	0	0	0	+			
0	+	+	+	+	0	0	0	+			
Theocalcin, 4.5 Digitalis, 1.8	0	0	0	0	0	0	0	+			
Theocalcin, 4.5 Theocalcin, 4 Theocalcin, 4	0	+	0	0	0	0	0	+			
Theocalcin, 3	0	0	0	+	0	0	0	+			
0	+	+	0	+↓	0	0	0	+	5.0	92	
0	..	..	..	..	..	..	..	+			
0	0	+	0	+↑	0	0	0	+			
0	0	+↑	0	+	0	0	0	+	5.1	102	
0	0	0	0	0	0	0	0	+	5.3	106	
.....	0	0	0	0	0	0	0	0			
Digitalis, 0.2; ammonium chloride, 3	0	+	+	+	0	0	Rt.	+	4.3	80	No digitalis was given between Dec. 28, 1935, and Jan. 27, 1936; mercupurin (a mercurin-theophylline preparation) (2 cc.) was given intravenously on Jan. 26, 1936; no digitalis was given between March 5 and April 27, 1936; on March 18, 1937, the patient was pregnant; therapeutic abortion, by means of miniature cesarean section, was performed on December 3
Ammonium chloride, 3	0	+↓	+	+	0	0	Rt.	+			
.....	±	0	+↓	+	0	0	Rt.	+	3.9	77	
0	0	+	+	+	0	0	Rt.				
Digitalis, 1.8											
0	0	0	+	+	0	0	Rt.	+			
Digitalis, 0.2	0	+	+	+	±	0	Rt.	+			
0	0	+	+	+	±	0	Rt.	±	4.4	82	
0	0	0	+↑	+↑	0	0	0	0	4.3	84	
0	0	0	+↑	0	0	0	0	0	4.3	100	
0	0	0	0	0	0	0	0	0	4.0	80	
0	0	0	0	0	0	0	0	0	4.1	87	
0	+	+	+	+	+	0	Rt.	+	5.7	104	Mercupurin (a mercurin-theophylline preparation) (2 cc.) was given intravenously on Feb. 1, 1937
0	0	+	+	+	+	0	Rt.	+	5.2	100	
Ammonium chloride, 3	0	+	+	+	+↑	0	Rt.	+	5.0	100	
Ammonium chloride, 3	..	..	..	..	..	..	..	+			
Ammonium chloride, 3	0	0	0	+	±	0↑	Rt.	+	5.6	110	
Urea, 30	0	±	+	+	+	+	Rt.	+			
Digitalis, 0.1	0	+	+	+	+	+	Rt.	+	5.1	122	Mercupurin (a mercurin-theophylline preparation) (2 cc.) was given intravenously on Sept. 21, 1936; theocalcin (1.5 Gm. three times daily) and ammonium chloride (1 Gm. twice daily) were also being given
Digitalis, 0.1	0	+	0	+	±	+	Rt.	+	5.3	104	
Digitalis, 0.2; ammonium chloride, 3											
Digitalis, 0.2; ammonium chloride, 3	0	+	0	+	0	+↑	Rt.↑	+	4.0	78	
Digitalis, 0.2; aminophylline, 0.3	+	+↓	+	+	+	+↓	Rt.↓	+	4.3	96	
Digitalis, 0.2; urea, 45	+	+	+	+	+?	+	Rt.	+			
0	+	+	+	+	+	+	0	+	5.5	110	Mercupurin (a mercurin-theophylline preparation) (2 cc.) was given intravenously on Nov. 17, 1937; theocalcin (1 Gm. three times daily) and ammonium chloride (1 Gm. three times daily) were also being given
Theocalcin, 4.5	0	0	+↓	+↓	+↓	+	0	+			
0	0	+	0	+	+	+↓	0	+	4.8	90	
Ammonium chloride, 3	0	0	0	+	±	+↓	0	+	4.9	86	
.....	0	0	0	+↓	±	0	0	+	5.9	96	
Ammonium chloride, 3; theocalcin, 3	0	0	0	+	0	0	0	±			
Ammonium chloride, 3	±	±	0	+	±	+	0	+			
Digitalis, 0.1; ammonium chloride, 6	0	+	0	+	0	±	0	+	5.4	114	Mercupurin (a mercurin-theophylline preparation) (2 cc.) was given intravenously on Feb. 4, 1937
Digitalis, 0.1; ammonium chloride, 6	0	+↓	±	+↓	0	0	0	+			
Digitalis, 0.1; ammonium chloride, 6	+	+	±	+	0	0	0	+	4.7	94	
Digitalis, 0.1; ammonium chloride, 6	0	±	0	+	0	0	0	+			
0	0	+	0	+	0	0	0	+	5.4	118	This patient was referred for study by Dr. Ralph Boots
0	0	0	0	0	0	0	0	+	5.8	95	Referred by Dr. Richmond L. Moore¶

‡ In this report 14.5 Gm. of hemoglobin was taken as equivalent to 100 per cent.

§ "Resting" and not "basal" measurements.

¶This patient had suffered from purulent pericarditis for ten months before these observations were made, and this had been cured by surgical drainage (Moore, R. L.: Ann. Surg. **102**: 980, 1935).

There were limitation of motion of the cardiac chambers and fixation of the heart on fluoroscopic examination. In 4 cases (cases 1, 5, 7 and 8) calcification was observed. After operation the extent of contraction increased in all cases.

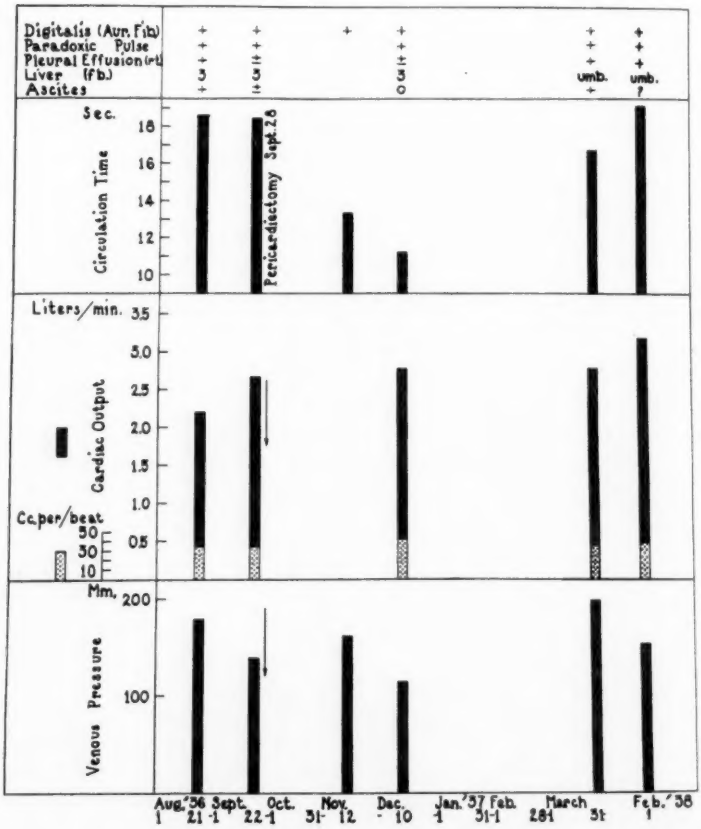

Fig. 5.—In this figure are plotted data relating to case 5.

The size and shape of the cardiac silhouette [15] was not uniform. In 7 cases it was moderately large (cases 2 [fig. 10], 3, 4, 5 [fig. 11], 7, 8 [fig. 12] and 9) and in 2 conspicuously small (cases 1 [fig. 13]

15. It is recalled that the cardiac silhouette includes the shadow of the heart together with the thickened pericardium and that the cardiac size may be small though the shadow is large.

and 6). Lateral views revealed calcification in 4 cases (cases 1 [fig. 3], 5 [fig. 11], 7 and 8 [fig. 12]). In 2 of the cases (cases 1 [fig. 3] and 6) in which operation was performed there was a decrease in the size of the heart, in 3 (cases 2 [fig. 10], 3 and 7) there was an increase and in the other 2 (cases 4 and 5 [fig. 11]), there was no change.

MEDICAL TREATMENT

The medical treatment has been similar to that used in cases of heart failure, with the exception of the use of digitalis. The patients were given a low salt diet (2 Gm. daily), and the intake of fluid was limited to 1,200 cc. Liberal amounts of protein were given because of the low value for serum protein in 2 cases and in order to maintain the level of the serum protein in the others.

Digitalis was given to 2 patients (cases 5 and 7) exhibiting auricular fibrillation, to keep the cardiac rate slow. We were unable to attribute any particular diuretic effect to its use in these cases.

We found mercupurin (a mercurin-theophylline preparation) the most satisfactory drug to use to mobilize fluids (Stewart and Wheeler [16]). It was usually given in 2 cc. doses intravenously at three day intervals. Ammonium chloride (3 Gm. a day) was given to certain patients to enhance the diuretic effect. Theocalcin (4.5 Gm. daily) was given at other times. Urea (50 per cent solution) was given twice a day in 30 cc. doses to 1 patient. Aminophylline (0.1 Gm. three times a day) was used on other occasions. Abdominal and thoracic paracenteses were used if other measures were not effective. Pericardiectomy was carried out when the patient had attained a suitable state; afterward the drugs for mobilization of fluid were continued if necessary. Giving mercupurin in case 6 resulted in only slight diuresis before operation; after pericardiectomy, however, 5,000 cc. of urine was secreted on the day of the injection. Diuretics were given after operation as long as necessary. They were not required in cases 1 and 2, while in case 3 mercupurin (a mercurin-theophylline preparation) was required for twelve months after operation. Two patients (cases 4 and 6) became ambulatory with weekly injections of mercupurin. In case 5 the use of urea maintained the output of urine to amounts that prevented too great an accumulation of fluid, and the patient was able to carry on her household acivities.

CLINICAL FEATURES

The histories of the 9 patients we have observed, together with the correlation of the manifestations on physical examination and the measurements of the circulation, are as follows:

16. Stewart, H. J., and Wheeler, C. H.: The Use of Mercupurin in the Treatment of Congestive Heart Failure and in the Mobilization of Excess Body Fluid, Am. Heart J. **14**:526, 1937.

TABLE 2.—*Summary of Clinical Manifestations in Nine Cases of Chronic Constrictive Pericarditis, Pericardial Resection Being Performed in Seven Cases**

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	
Age	15 years	36 years	30 years	20 years	44 years	38 years	58 years	29 years	13 years	
Sex	Female	Male	Female	Male	Female	Female	Male	Male	Male	
History of rheumatic infection	Present	Absent	Absent	Absent	Present	Absent	Absent	Absent	Absent	2
Evidence of valvular heart disease	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	0
History of tuberculous infection	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	1
History of nonspecific pulmonary infection just before onset of symptoms	Absent	Present	Absent	Absent	Absent	Present	Absent	Absent	Present	3
History of pericarditis or pericardial effusion	Absent	Present	Absent	Present	Absent	Absent	Absent	Absent	Present	3
Cause found at operation	Unknown	Unknown	Tuberculosis	Unknown	Unknown	Unknown	.....	.....	.....	
Chief symptoms†	Swelling of abdomen, loss of weight and dyspnea	Dyspnea, edema, ache in epigastric region and "fulness" in head	Dyspnea, weakness and swelling of abdomen	Swelling of abdomen and dyspnea	Swelling of abdomen	Swelling of ankles and dyspnea	Swelling of ankles and dyspnea	Ache in epigastric region	None	
Signs of heart failure before operation										
Dyspnea	Absent	Present	Present	Doubtful	Absent	Present	Absent	Absent	Absent	3+
Cyanosis	Present	Present	Present	Doubtful	Present	Present	Doubtful	Present	Absent	6+
Distention of neck veins	Present	Present	Present	Present	Present	Present	Present	Present	Absent	5
Rales	Absent	Absent	Present	Present	Doubtful	Doubtful	Doubtful	Absent	Absent	2+
Fluid in chest	Absent	Absent	Present	Present	Present	Present	Absent	Absent	Absent	4
Enlarged liver	Present	Present	Present	Present	Present	Present	Present	Present	Absent	5
Ascites	Present	Absent	Present	Present	Present	Doubtful	Doubtful	Absent	Absent	4+
Edema	Absent	Absent	Present	Absent	Present	Present	Doubtful	Absent	Absent	3+
Rhythm†	N.S.R.	N.S.R.	N.S.R.	N.S.R.	A.F.	N.S.R.	A.F.	N.S.R.	N.S.R.	
Paradoxic pulse	Present	Present	Present	Present	Present	Present	Present	Present	Present	9
Blood pressure	Low	Low	Low	Low	Normal	Normal	Slightly high	Low	Normal	

Low pulse pressure	Present	Present	Present	Present	Absent	Absent	Absent	Present	Absent	5
Venous stasis in infra-red photograph	Present	Present	Present	Present	Doubtful	Present	Absent	.....	.....	5 ↓
Fluoroscopic examination of heart										
Decreased pulsations	Present	Present	Present	Present	Present	Present	Present	.....	.....	7
Shift of heart with change in patient's position	.....	Very slight	.....	.....	Moderate	None	.....	.....	None	
Size of heart in roentgenogram	Very small	Large	Slightly enlarged	Large	Large	Small	Large	Slightly enlarged	Slightly enlarged	9 ↑
Calcification of pericardium										
In roentgenogram	Present	Absent	Absent	Absent	Present	Absent	Present	Present	Absent	4
At operation	Present	Absent	Absent	Absent	Present	Absent	Present	.....	.....	3
On microscopic examination§	Present	Present	Absent	Absent	Present	Present	Present	.....	.....	5
Electrocardiogram‖										
QRS, leads I to III	Low ampl.	Low ampl.	Low ampl.	Low ampl.	Low ampl.	Low ampl.	Low ampl.	Low ampl.	Normal ampl.	8 ↓
T wave	I to III, low ampl.; II and III, cove shaped	1 and II, negative	I to III, low ampl.	I to II, cove shaped	I to III, diphasic	III, low ampl.	I to III, low ampl.; diphasic	II and III, negative; cove shaped	I to III, normal ampl.	
Axis deviation	Slight, right	Right	Slight, right	Slight, left	Slight, right	Slight, left	Right	Slight, right	Slight, left	6 RAD
Shift of electrical axis	37 degrees	None	11 degrees	11 degrees	35 degrees	None	26 degrees	None	.....	
Venous pressure	Increased	Slightly increased	Increased	Increased	Increased	Increased	Increased	Increased	Slightly increased	9 ↑
Circulation time	Increased	Increased	Increased	Increased	Increased	Increased	Increased	Increased	Normal	8 ↑
Cardiac index	Decreased	Decreased	Decreased	Decreased	Decreased	Normal	Decreased	Decreased	Decreased	8 ↓
Cardiac output per beat	Decreased	Decreased	Decreased	Decreased	Decreased	Normal	Decreased	Decreased	Decreased	6 ↓
Plasma protein value	Normal	Normal	Normal	Normal	Decreased	Decreased	Normal	.....	.....	
Duration of symptoms before operation	5 yr. 6 mo.	2 yr. 8 mo.	4 mo.	1 yr. 3 mo.	2 mo.	6 yr.	6 yr.	9 yr.	10 mo.	
Result of medical treatment	Poor	Good	Poor	Poor	Fair	Poor	Fair	.....	.....	
Result of operation	Cured	Cured	Cured	Improved	Improved	Improved	Convalescent from operation	.....	.....	
Time since operation	1 yr. 9 mo.	1 yr. 4 mo.	2 yr. 2 mo.	1 yr. 3 mo.	1 yr. 6 mo.	8 mo.	1 mo.	.....	.....	

* Throughout this table leaders in a column indicate that the data were not available. For further details the case histories should be consulted.
† The symptoms are listed in the order of severity.
‡ N.S.R. indicates normal sinus rhythm, and A.F., auricular fibrillation.
§ This refers to the examination of the pericardium excised at operation.
‖ Ampl. indicates amplitude.

Case 1.—A. B., a girl aged 15 years, was admitted to the hospital on May 14, 1936. She suffered from acute polyarthritis when 6 years old. Four years later, swelling of the abdomen appeared. At exploratory laparotomy the diagnosis was tuberculosis of the peritoneum. Although swelling of the abdomen persisted, the patient felt well until four years later. Four months before admission to the hospital she suffered from a progressive increase in the size of the abdomen, dyspnea on exertion, weakness, anorexia and emaciation. On entry, emaciation, evidence of retarded development, moderate cyanosis, distention of the veins of the neck together with prominence of the superficial veins over the surface of the entire body, marked enlargement of the liver, signs of a large amount of ascitic fluid and a radial pulse of paradoxic type were observed. The heart sounds were faint. The blood pressure was 88 systolic and 52 diastolic. Other data are shown in table 2. With medical therapy, no appreciable change occurred.

The pericardium was resected on June 5. The heart was constricted within a greatly thickened, calcified pericardium whose two layers were adherent. Microscopic examination did not disclose the cause. Improvement was rapid without medication. On June 23 the radial pulse was no longer paradoxic, and all the signs of heart failure were much less marked. The patient was discharged and sent to the clinic on July 3. On August 3 the signs of ascites had disappeared. Enlargement of the liver was the only sign of congestion on October 20, but the organ was no longer palpable on December 4. One year and nine months after operation there was marked improvement in nutrition, with progress in development. She had been indulging in unrestricted physical activity, without symptoms and without recurrence of heart failure.

Case 2.—W. M., a man aged 36 years, was admitted on July 26, 1935. Sixteen months earlier he suffered from an acute pulmonary infection associated with acute pericarditis. At the end of three months he experienced increasing dyspnea on exertion, orthopnea, a constant ache in the epigastric region, swelling of the ankles and weakness and at the end of twelve months was confined to bed. On admission to the hospital he showed marked dyspnea, cyanosis, orthopnea, distention of the veins of the neck, rales at the bases of both lungs, marked enlargement of the liver, signs of a small amount of ascitic fluid, marked pitting edema of the lower part of the legs and a paradoxic radial pulse. The rhythm of the heart was regular. The blood pressure measured 122 systolic and 90 diastolic. Other data are shown in table 2. With medical therapy marked improvement occurred, and three months later enlargement of the liver was the only sign of heart failure. The diagnosis was pericardial effusion with resorption. At the time of his discharge, on November 9, it was thought that he suffered from chronic constrictive pericarditis. A year later the symptoms and signs of heart failure recurred, and he returned to the hospital (Nov. 9, 1936).

After medical preparation the pericardium was resected (November 25). The two layers of the pericardium were adherent and thickened and constricted the heart. Microscopic examination did not reveal the cause. Calcification was noted only on microscopic examination. The day after operation the distention of the veins of the neck was less. Four weeks later diuresis occurred spontaneously without drugs. On December 30 moderate cyanosis, distention of the veins in the right side of the neck and moderate enlargement of the liver were the only signs of heart failure; the radial pulse was only slightly paradoxic. The patient was discharged on December 30. One month later he indulged in ordinary physical

exertion, without distress. On March 15, 1937, slight enlargement of the liver was the only sign of heart failure. One and one-third years after operation the patient was actively at work and free from symptoms and signs of heart failure.

Case 3.—A. R., a woman aged 29 years, was admitted on Dec. 3, 1935. Twelve months before entry, during pregnancy, she experienced rapidly progressive weakness. In the fifth month of pregnancy she suffered from fever of unknown origin. Signs of heart failure and a paradoxic radial pulse developed during the sixth month of pregnancy. After delivery of a living infant in the eighth month of pregnancy, she continued to suffer from dyspnea on exertion, swelling of the ankles and weakness, with the addition of orthopnea and a progressive increase in the size of the abdomen. When admitted to the medical service four months later she showed: dyspnea, cyanosis, orthopnea, marked distention

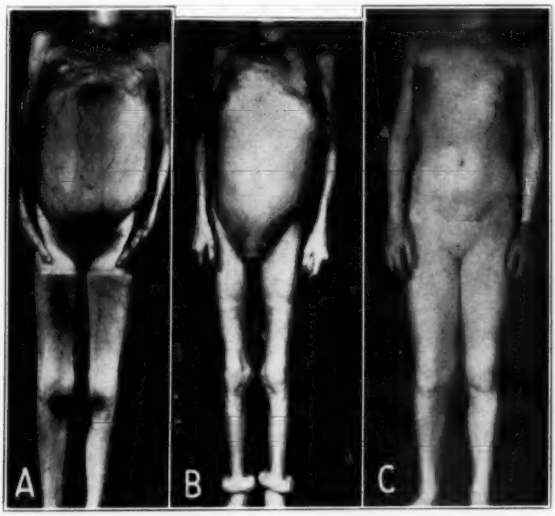

Fig. 6.—Infra-red photographs of A. B. (case 1) showing the change in the venous bed after pericardial resection. *A* was taken on May 20, 1936, before operation (performed on June 8); *B*, on June 29, about three weeks after operation, and *C*, on April 6, 1937, about ten months after operation, when the patient was "cured."

of the veins of the neck, signs of a large amount of fluid in the right pleural cavity, many moist rales at the base of the left lung, marked enlargement of the liver, signs of a large amount of ascitic fluid and moderate edema of the lower part of the legs. The radial pulse was paradoxic. The blood pressure measured 112 systolic and 76 diastolic. The heart sounds were faint. The rhythm of the heart was regular. Other data are shown in table 2. By medical means and seven thoracenteses (right), the dyspnea, orthopnea, signs of ascites and edema of the legs disappeared; and the signs of fluid in the right pleural cavity, the number of rales at the base of the left lung and the size of the liver all decreased.

On Jan. 28, 1936, the pericardium was resected. The heart was constricted within a thickened pericardium, and the two layers, which were firmly adherent, showed active tuberculous infection without calcification. After operation, mercupurin (a mercurin-theophylline preparation) induced greater diuresis than before. The distention of the veins of the neck decreased, but the other signs of heart failure did not change significantly. The radial pulse remained paradoxic. The patient was discharged on March 5. She returned to the clinic weekly for injections of mercupurin. The symptoms and signs of heart failure gradually disappeared. By July 6 the patient was free from cardiac symptoms, although indulging in moderate physical exertion. By August 28 the radial pulse had lost its paradoxic

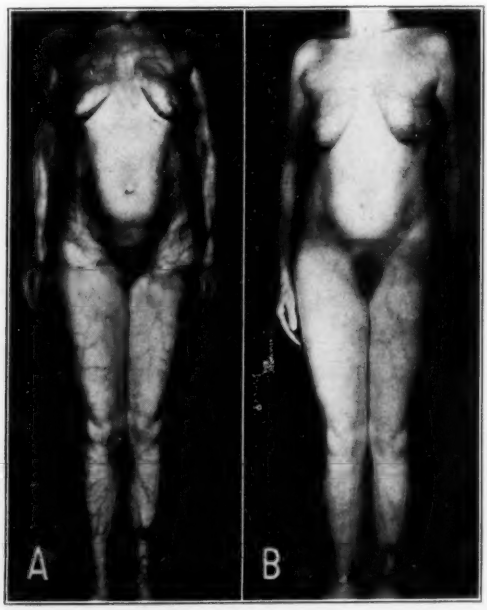

Fig. 7.—Infra-red photographs of A. R. (case 3). None were taken before operation. *A* was taken on Dec. 9, 1936, about ten months after operation (performed on January 28), and *B*, nearly one year later, on Nov. 30, 1937. In this case the improvement was slow, but the patient is now "cured."

characteristics. On December 9 a few rales at the base of the left lung, slight distention of the veins in the right side of the neck and moderate enlargement of the liver were the only signs of heart failure. On December 28 the use of drugs, including mercupurin was discontinued. By March 18, 1937, all the signs of heart failure had disappeared. The patient was engaging in unrestricted physical exertion, without symptoms. Two years and two months after operation the patient was still in excellent health.

Case 4.—J. McC., a man aged 20 years, was admitted on Nov. 18, 1936. Fourteen months earlier he suffered from pericardial effusion. Three months later he recovered and felt well until nine months before entry, when he experienced dyspnea on exertion, orthopnea, swelling of the ankles and recurrence of fever. The radial pulse was paradoxic. He again exhibited a large amount of pericardial effusion. After resting two months he attempted activity. The symptoms recurred, and, in addition, swelling of the abdomen appeared. Four months later he was admitted to the hospital, exhibiting slight dyspnea, slight cyanosis, moderate distention of the veins of the neck, rales at the base of the left lung, signs of a

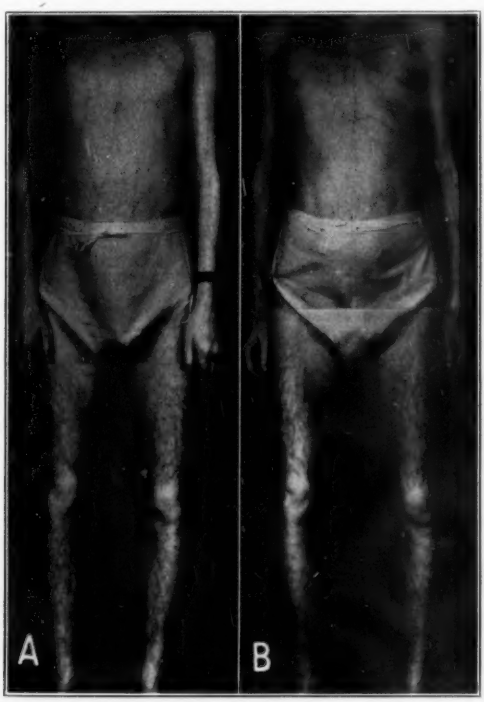

Fig. 8.—Infra-red photographs of J. McC (case 4). *A* was taken on Nov. 19, 1936, before operation (performed on December 21), and *B*, on March 29, 1937, more than three months after operation, when the patient was improved.

moderate amount of fluid in the right pleural cavity, marked enlargement of the liver, signs of a moderate amount of ascitic fluid and a paradoxic pulse. The blood pressure measured 98 systolic and 70 diastolic. Other data are shown in table 2. With medical therapy, slight improvement occurred.

On December 21 the pericardium was resected. The heart was constricted within a tough, fibrous pericardium, the two layers of which were closely fused. Microscopic examination revealed neither calcification nor the etiology. After opera-

tion mercupurin (a mercurin-theophylline preparation) induced more marked diuresis. A significant change in the signs of heart failure was not apparent on discharge, on March 3, 1937. The patient returned weekly for injections. By March 28 he was indulging in ordinary physical exertion, without symptoms. Slight distention of the veins of the neck, signs of a small amount of pleural effusion on the right side and of a small amount of ascitic fluid, moderate enlargement of the liver and a radial pulse of paradoxic type were present. One year and three months after operation the patient was indulging in ordinary physical exertion, commuting to college daily and leading a normal existence. The symptoms had not recurred, and the signs of heart failure appeared to be diminishing. He had been much improved by the operation but a "cure" had not been obtained.

Fig. 9.—Infra-red photographs of J. S. (case 6). *A* was taken on May 26, 1937, when the patient was in her best state before operation (performed on June 17); *B*, on November 19, when she was free from signs of failure after operation, and *C*, on Jan. 28, 1938, when she was ambulatory.

Case 5.—P. A., a woman aged 44 years, was admitted on Aug. 12, 1936. She had suffered from "pneumonia" and from an attack of acute polyarthritis at 20 and 30 years of age, respectively. Ten years before entry she observed swelling of the ankles occasionally. Two months before entry she experienced slight dyspnea on exertion, progressive increase in the size of the abdomen and persistent swelling of the ankles. She was given digitalis, without apparent benefit. Slight cyanosis, distention of the veins of the neck, signs of a moderate amount of fluid in the right pleural cavity, marked enlargement of the liver, signs of a large amount of ascitic fluid, massive pitting edema of the lower part of the legs and thighs, and a radial pulse of paradoxic type were present on entry. Auricular

fibrillation was noted. The blood pressure measured 110 systolic and 70 diastolic. Additional data are shown in table 2. With medical therapy the ascites disappeared, and the edema of the legs decreased markedly.

On September 28 the pericardium was resected. The heart was constricted within a markedly calcified pericardium whose two layers were closely fused and were adherent to the surface of the myocardium. The etiology was not discovered. After operation ammonium chloride and maintenance doses of digitalis were given daily, and mercupurin was used. On December 19 slight distention of the veins of the neck, signs of a small amount of fluid at the base of the right lung, marked enlargement of the liver, signs of a small amount of ascitic fluid and slight edema of the ankles were still observed. The radial pulse was still of paradoxic type. The patient was discharged on December 19. She received mercupurin during the first year, but its use was discontinued because of nausea and vomiting. After that she was given urea (30 Gm. daily). For one and

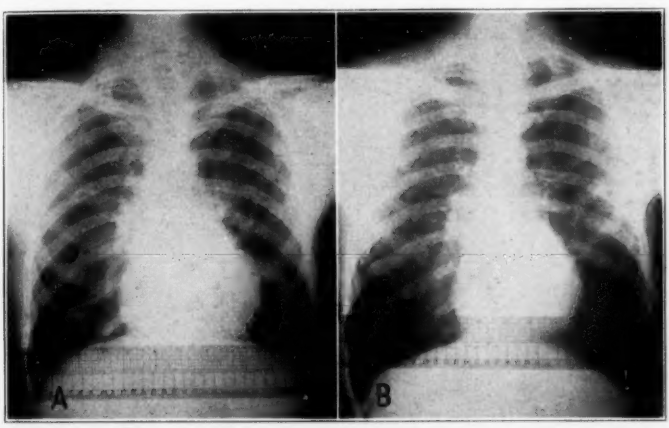

Fig. 10.—Roentgenograms of W. M. (case 2) taken at a distance of 2 meters. *A* was taken on Nov. 11, 1936, before operation (performed on November 25), and *B*, on April 1, 1937, after operation. The size of the cardiac silhouette is seen to have decreased.

one-half years after operation the improvement was slow but definite. The patient could do housework without symptoms, and the signs of heart failure were not increased.

Case 6.—J. S., a woman aged 38 years, was admitted on May 24, 1937. Six years earlier she suffered from an illness characterized by fever, cough and pain in the left scapular region on inspiration. These symptoms confined her to bed for three months. When she attempted activity she suffered from dyspnea on exertion, orthopnea and swelling of the ankles and abdomen. She was given digitalis and diuretics. Five and one-half years before entry thyroidectomy was performed. Her symptoms, however, became slowly more severe. On entry moderate dyspnea, orthopnea and cyanosis, distention of the veins of the neck, a few moist rales at the bases of both lungs, marked enlargement of the liver, signs

of a small amount of ascitic fluid, massive brawny edema of the lower part of the legs and thighs, and a radial pulse of markedly paradoxic quality were present. The blood pressure measured 130 systolic and 78 diastolic. The rhythm of the heart was regular. Other data are shown in table 2. With a medical regimen dyspnea and cyanosis disappeared, and the number of rales at the bases of the lungs, the size of the liver, the signs of ascites and the edema of the legs decreased.

On June 17 the pericardium was resected. The parietal pericardium was leathery, inelastic and loosely adherent to the visceral layer. Calcification was noted only on microscopic examination. The cause was not discovered. During the postoperative period, mercupurin (a mercurin-theophylline preparation) induced much more marked diuresis than formerly. On August 28 moderate enlargement of the liver and slight edema of the ankles only were present. The patient was discharged. She engaged in moderate physical exertion; and although mercupurin (a mercurin-theophylline preparation) was given weekly, signs of congestion increased slightly. Eight months after operation slight dyspnea, slight cyanosis, moderate distention of the veins of the neck, marked enlargement of the liver,

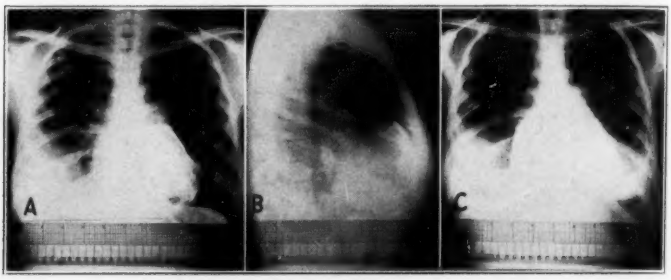

Fig. 11.—Roentgenograms of P. A. (case 5). *A* and *B* were taken on Sept. 22, 1936, before operation (performed on September 28), and *C* was taken on December 10, after operation. Calcification can be seen in *A* as well as in *B*, a lateral view.

signs of a small amount of ascitic fluid, marked edema of the legs and the paradoxic radial pulse were still present. The patient's condition was, however, much improved (see the discussion of this case under the heading "Comment") over her preoperative condition, and she was ambulatory.

Case 7.—R. S., a man aged 58 years, was admitted on Jan. 17, 1938. He was accepted for life insurance in 1929. Six years before admission to the hospital he experienced dyspnea on exertion and swelling of the ankles. The diagnosis was "hypertensive heart disease with heart failure." A roentgenogram of the heart at this time showed "marked dilatation of the left ventricle." He was given digitalis daily and stopped working; but in the six years preceding admission to the hospital the severity of his symptoms increased slowly and his activity became greatly limited. At entry, slight cyanosis, moderate distention of the veins of the neck, a few moist rales at the bases of both lungs, marked enlargement of the liver, signs of a small amount of ascitic fluid, slight edema of the ankles and the paradoxic radial pulse were present. The heart was enlarged to the left. The

rhythm was totally irregular. The blood pressure measured 155 systolic and 100 diastolic. Other data are shown in table 2. With a medical regimen the signs of heart failure diminished. Pericardiectomy was discussed with the patient. He was discharged on February 27, for consideration of operation. Although he indulged in slight physical exertion and mercupurin (a mercurin-theophylline preparation) was given weekly, dyspnea and swelling of the ankles recurred. The patient requested that pericardial resection be done and was readmitted on April 11. The signs of heart failure were essentially the same as at the time of the first entry. With medical treatment improvement occurred.

On April 26 the pericardium was resected. The two layers of the pericardium were everywhere adherent and the base and the right side of the heart were encased in a rigid, calcified shell. The cause was not disclosed on microscopic examination. His convalescence was slightly retarded by extravasation of sero-

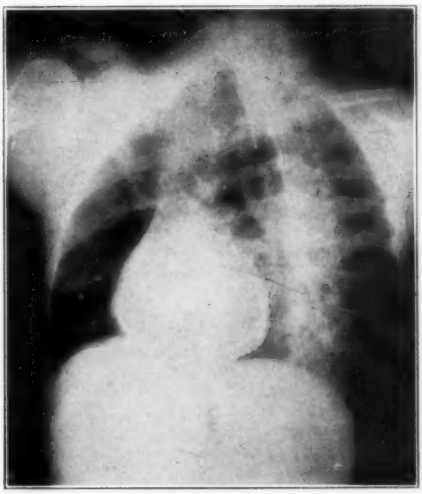

Fig. 12.—A roentgenogram of C. G. (case 8), taken from an oblique angle (June 1, 1935). A wide rim of calcification is shown surrounding the heart.

sanguineous fluid between the heart and the soft tissue flap, which finally discharged at the lower angle of the incision. It is not yet possible to estimate the result of pericardiectomy.

Case 8.—C. G., a man aged 29 years was admitted on June 5, 1935. Enlargement of the liver had been discovered nine years before. He exhibited no cardiac symptoms at this time and was not told that he had "heart trouble." Six years before entry he had "double pneumonia," and in the two years preceding entry he had three other attacks of "pneumonia," at intervals of about eight months. For four years he experienced aching and a sense of pressure in the epigastric region, which were exaggerated by exertion. These symptoms became more severe, and slight dyspnea on exertion and blueness of the lips appeared. When

admitted he showed marked cyanosis, distention of the veins of the neck, marked enlargement of the liver and a radial pulse of paradoxic type. The blood pressure measured 90 systolic and 70 diastolic. Other data are shown in table 2.

CASE 9.—I. F., a boy aged 13 years, was admitted on Dec. 10, 1934. He had enjoyed excellent health until ten months prior to entry when he had "pneumonia" followed by "empyema of the pericardium." Four months later the pericardium was opened to secure drainage. After this the patient improved rapidly, gained 40 pounds (18 Kg.) in weight and was cured. He was referred to the hospital for our studies. There were no signs of heart failure, but the radial pulse was paradoxic. The heart exhibited no abnormal signs. The blood pressure measured 116 systolic and 66 diastolic. Other data are shown in table 2.

Comment.—From the summary (table 2) of the data for the 9 patients whom we have studied, it appears that the following manifestations contribute to the recognition of this syndrome: Signs of congestive heart failure are present in the absence of the usual, more

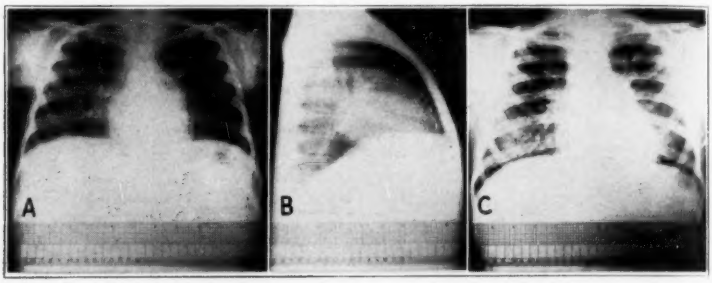

Fig. 13.—*A*, roentgenograms of A. B. (case 1). *A* and *B* were taken on June 2, 1936, before operation (performed on June 5), and *C* was taken on April 6, 1937, after operation. Calcification is shown in the lateral view (*B*), before operation.

common causes. Organic valvular lesions are conspicuously absent. Enlargement of the liver and ascites are usually present. Edema and pleural effusion occur, but less frequently. Distention of peripheral veins is a constant finding. The cardiac silhouette may be small, moderately enlarged or approximately normal. The point of maximal impulse may not shift. A paradoxic pulse was present in every case. The blood pressure is usually low and the pulse pressure small. Decrease or absence of motion of the several chambers of the heart may be observed. Calcification may be seen in the fluoroscope and in roentgenograms, though oblique views may be necessary to demonstrate it. It may be recalled, however, that calcification may be present without giving rise to obstruction. The electrocardiographic characteristics appear to be low amplitude of the QRS and T waves (fig. 14). The T wave in leads I and II may be "cove" shaped. The electrical axis may not shift or may shift

only slightly (fig. 14); too much emphasis is not to be placed on this finding, however. Slight right or slight left axis deviation may be present. A normal rhythm is usually present, though auricular fibrillation occurs in a few cases. Taking into consideration the operative procedures and the changes in the clinical state of the patient, it may be said that marked changes do not occur in the electrocardiogram after operation. Since 3 of our patients were observed during the stage of pericardial effusion, through the stage of absorption and then through the stage of constriction, this sequence is not uncommon. Patients suffering from pericardial effusion, in the absence of rheumatic valvular disease, should be observed continuously to be prepared for this development. We have been impressed with the absence of the usual rheumatic manifestations in these cases in which constriction has occurred, a point to which White [1] has already directed attention.

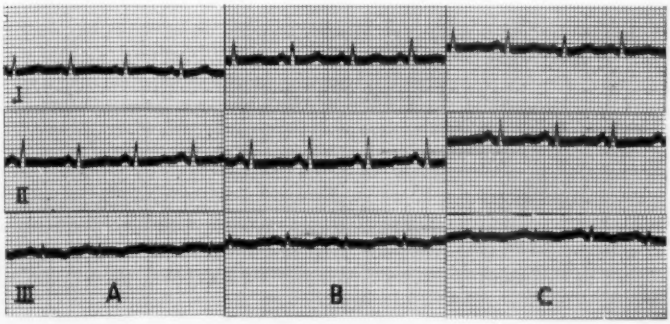

Fig. 14.—Electrocardiograms of J. S. (case 6) taken on May 26, 1937, before operation (performed on June 17). *A* was taken when the patient was lying on her back; *B*, when she was lying on her right side, and *C*, when she was lying on her left side. It is seen that the electrical axis remained practically fixed.

OPERATIVE TECHNIC

In the 7 cases in which operation was performed, ether anesthesia was used. The third, fourth, fifth and if necessary the second or sixth costal cartilages and the adjacent part of the ribs were resected on the left side.[17] The pericardium was incised over the left ventricle, mobilized and excised, after which a similar procedure was carried out over the right ventricle. The left ventricle was decompressed first; so it was ready to receive the increased amount of blood that was anticipated from decortication of the right ventricle. The pericardium was resected from as much of the anterior surface of the heart as possible without too great danger to the patient. The cardiac muscle herniated through the

defect in the pericardium in all cases. The skin-muscle flap was closed in layers. Since the periosteum of the ribs was left in place, regeneration and reformation of the bony part of the thorax occurred. Convalescence was rapid. The postoperative care was a continuation of the medical therapy; in 2 cases only was an oxygen tent used for a few hours after operation.

In 3 of the 7 cases in which operation was performed, "cure" has been obtained, and in 3 cases the condition has been improved. It is too early to foresee the result in the seventh case. These operative results, so far as they go, are an improvement over those previously reported. From the standpoint of the "cures" obtained, they are almost identical with those reported by Schmeiden, Churchill and Beck in cases in which the patients survived operation.[17]

COMMENT

Our studies show that the syndrome of chronic constrictive pericarditis is associated with decrease in the cardiac output per beat and per minute, rise in the venous pressure and slowing of the velocity of blood flow. The alteration in the circulation appears to be dependent on two defects. In the first place, the filling of the heart is compromised. This is apparent clinically on fluoroscopic examination in the finding of decreased filling of the heart in diastole, as well as when the heart is exposed at operation. In the second place, contraction is impaired, since on fluoroscopic examination and at operation decreased contractions of the heart are observed. These two defects result in a decrease in the cardiac output per minute and per beat and a piling up of blood on the venous side, which is observed objectively in the rise in venous pressure. The clinical manifestations of the disease appear to be associated with these alterations of the circulation. When clinical improvement or cure followed release of the heart by pericardial resection, parallel alterations of the circulation occurred toward or to normal levels, owing to greater filling of the heart in diastole and an increased discharge of blood in systole. These studies show parallelism between the physical signs and the objective circulatory impairment in these cases. They do not, however, elucidate the mechanism of certain signs which occur. That distention of veins and enlargement of the liver occur is to be expected. On the other hand, there has been no explanation of the occurrence of edema or of pleural effusion in certain cases and not in others. Venesection appears to be contraindicated in the presence of this syndrome, since the elevated venous pressure may represent the head of pressure which is required to maintain the circulation.

17. Heuer, G. J., and Stewart, H. J.: The Surgical Treatment of Chronic Constrictive Pericarditis, to be published.

In case 6 the pattern of the measurements of the circulation did not conform with the pattern exhibited in the others; in this case the cardiac output per minute and the cardiac index were normal before operation (table 1). Improvement after operation, though marked, has now become stationary; measurements of the circulation did not alter significantly. There are several factors which may contribute to the deviation of the pattern exhibited by this patient from that of the others. In the first place, she had been subjected to partial thyroidectomy six years earlier, when it was thought that the signs of cardiac failure were due to hyperthyroidism. In the second place, the level of the serum protein has remained low. The patient may, in addition, exhibit vitamin deficiency; it did not seem justifiable, however, in the evaluation of pericardial resection to test this hypothesis until there was stabilization after pericardiectomy. The effect of thiamin chloride is now being observed. It is likely that the obstruction was removed at operation, because the venous pressure has fallen to normal limits and the size of the cardiac shadow has increased.

Three of these patients first came under observation when pericardial effusion was present (cases 2 [fig. 2], 3 [fig. 3] and 4 [fig. 4]). Physical signs of obstruction (cases 3 and 4) and a change in the circulation characteristic of effusion (case 2) occurred. With absorption of fluid, the measurements of the circulation returned toward normal (case 2). Finally, when constriction began, signs of obstruction recurred, and impairment of the circulatory measurements appeared (case 2). The evolution of this process may require few (case 4) or many (cases 2 and 3) months.

Digitalis was given to 2 patients exhibiting auricular fibrillation to decrease the ventricular rate. The effect in 1 case (case 3 [table 1 and fig. 3]) after operation was similar to that observed in the presence of heart failure,[18] namely, an increase in cardiac output, a fall in venous pressure and shortening of the circulation time. Fluid in the right pleural cavity prevented measurement of the cardiac size. The effect of digitalis on the circulation in another case (case 2 [table 1 and fig. 2]) when pericardial effusion was present could not be evaluated with certainty because the studies intended for control were made four days before the drug was given; changes in the circulation not related to digitalis may have occurred during this time. The

18. (*a*) Stewart, H. J., and Cohn, A. E.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: III. The Effect on the Output in Normal Human Hearts; the Effect on the Output of Hearts in Heart Failure with Congestion, in Human Beings, J. Clin. Investigation **11**:917, 1932. (*b*) Stewart, H. J.; Deitrick, J. E.; Crane, N. F., and Wheeler, C. H.: Action of Digitalis in Uncompensated Heart Disease, Arch. Int. Med. **62**:569 (Oct.) 1938.

use of this drug appears to be contraindicated except when auricular fibrillation is present. In other investigations we have found that digitalis decreases the size of the heart [19] and increases the extent of ventricular contraction.[20] In the case of the compressed, constricted heart, to decrease its size may amount to increasing the obstruction; on the other hand, it is likely that systolic contraction is as complete as is possible with the thickened, perhaps calcified, pericardium adherent to the organ. Whether other effects of the drug might counterbalance these two contraindications cannot be stated. We were unable to attribute any beneficial effect to its use in the cases of auricular fibrillation, short of that associated with maintenance of the ventricular rate within bounds.

The effect of theocalcin was observed in 1 case (case 2) on several occasions (table 1 and fig. 2). The drug increased the cardiac output and the velocity of the blood flow and lowered the venous pressure, results similar to those previously recorded (Stewart and Cohn [18a]).

In case 3 a cure has apparently been obtained. The patient is well, without symptoms and signs, and is engaging in strenuous household duties. The measurements of the circulation have returned to normal (table 1 and fig. 3). When the second pregnancy since operation occurred there were increase of the arteriovenous oxygen difference and decrease of the cardiac output. Continuation of pregnancy appeared to be contraindicated. There was restoration of normal circulatory measurements after therapeutic abortion (fig. 3).

The speed of the circulation on the right and on the left side was studied by partition of the circulation time (table 3). There appeared to be no fixed pattern, the prolongation occurring on one side or the other or on both sides.

Three patients have been "cured," and the other 3 have been better since pericardiectomy (table 2). These results, though the number of cases is small, appear to be approximately the same as those recorded in the literature.[17] Analysis of the results favors the employment of pericardiectomy in the treatment of this syndrome.

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19. (*a*) Stewart, H. J.; Crane, N. F.; Deitrick, J. E., and Thompson, W. P.: Action of Digitalis in Compensated Heart Disease, Arch. Int. Med. **62**:547 (Oct.) 1938. (*b*) Stewart and Cohn.[18a] Stewart and others.[18b]

20. Cohn, A. E., and Stewart, H. J.: (*a*) Evidence That Digitalis Influences Contraction of the Heart in Man, J. Clin. Investigation **1**:97, 1924; (*b*) The Relation Between Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Normal Dogs, ibid. **6**:53, 1928; (*c*) The Relation Between Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Dogs in Which the Heart Is Enlarged, ibid. **6**:79, 1928.

The work of the heart was calculated by making use of the following formula:[21] $W = QR + \frac{wV^2}{2g}$, in which W equals the work done per beat, Q equals the stroke volume, R equals the mean arterial blood pressure in millimeters of mercury multiplied by 13.6, V equals the velocity of the blood at the aorta, w equals the weight of the blood and g equals the acceleration due to gravity. The last part of the formula, $\frac{wV^2}{2g}$, has been omitted. The work of the left ventricle per beat was increased after operation in all except 1 case (case 6 [table 1]).

TABLE 3.—*Data Relating to Velocity of Blood Flow (Circulation Time) in Five Cases of Chronic Constrictive Pericarditis*

			Circulation Time				
Case No.	Date	Venous Pressure, Cm.	A: Arm to Tongue (Decholin Sodium), Sec.	B: Arm to Lung (Ether), Sec.*	C: Lung to Respiratory Center (Carbon Dioxide), Sec.†	A Minus B, Sec.‡	Comment
2	1/28/38	9.2	19.2	5.5	15.0	13.7	Cured after operation
4	1/29/38	18.8	21.5	13.5	9.5	8.0	Improved after operation
5	2/ 1/38	15.3	19.2	6.0	13.5	13.2	Improved after operation
6	1/28/38	15.5	21.4	8.3	12.0	13.1	Improved after operation
7	1/19/38	22.3	29.8	12.5	17.0	17.3	No operation
	2/ 5/38	7.3	25.9	11.0	14.3	14.9	No operation
	4/12/38	25.9	35.5	....	12.0	....	No operation
	4/19/38	8.1	27.7	....	12.0	....	No operation
	6/13/38	16.4	28.9	....	13.5	....	Operation on 5/26/38

* Normal range, 3.5 to 8 seconds; average, 5.5 seconds (Hitzig, W. M.: Am. Heart J. **10**: 1080, 1935).

† This type of test was reported on by R. Gubner before the New York Heart Association on Feb. 1, 1938.

‡ The length of time recorded in column A minus that in column B should equal that in column C. The normal range is 4.5 to 9.5 seconds.

The work of the left ventricle has not been plotted against the cardiac volume in these cases, since it was impossible to estimate how much of the cardiac shadow was due to thickening of the pericardium.

SUMMARY AND CONCLUSIONS

An analysis of the clinical manifestations in 9 cases of chronic constrictive pericarditis has been given. In 7 of these cases partial pericardiectomy was performed. The presence of this syndrome should be considered when there are signs of congestive heart failure in the absence of the usual causes of failure. Three of the patients appear to be "cured," 3 others are greatly improved and the seventh is now convalescing from the operation. Our studies of the circulation have shown that this syndrome is associated with a decrease in the cardiac

21. Starling, E. H.: Principles of Human Physiology, ed. 6, Philadelphia, Lea & Febiger, 1933.

output per minute and per beat, a rise in the venous pressure and a slowing of the velocity of the blood flow. These alterations are related to the obstruction to the flow of blood into the heart, that is to say, to interference with diastolic filling, and to the interference with contraction, by the thickened, adherent pericardium. With the institution of pericardial resection and the subsequent clinical improvement, the measurements of the circulation undergo parallel changes toward or to normal. There is parallelism in these cases between the clinical manifestations and the objective measurements of the circulation. Our experience in these cases leads us to recommend surgical treatment.

ASCORBIC ACID IN BLOOD AND URINE AFTER ORAL ADMINISTRATION OF A TEST DOSE OF VITAMIN C

A SATURATION TEST

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Numerous methods have been proposed for the determination of vitamin C deficiency and for the estimation of the degree of saturation of the bodily tissues with vitamin C. The majority of these methods involve measuring the amount of ascorbic acid excreted in the urine in twenty-four hours (1) while the subject is taking his usual diet and (2) after the administration of a test dose of vitamin C. These procedures necessitate the complete cooperation of the patient in order to avoid loss of part of the specimen, and there is difficulty in preserving the urine against oxidation, with resultant loss of vitamin C. For these reasons the methods are not applicable to ambulatory patients. The best single test of vitamin C nutrition is considered by many to be the determination of the amount of reduced ascorbic acid in the blood during fasting. It gives an indication of the degree of tissue saturation but not a complete one, as there may be fluctuations with daily variation in the quantity of vitamin C in the diet. The aim of this study was to find a method of determining the state of vitamin C nutrition which would be applicable to ambulatory patients, which would require only a few hours to perform and which would avoid some of the difficulties that have been enumerated.

We studied 22 persons (25 tests being performed): 3 normal adults, 6 persons with psychoneuroses, 8 with chronic diseases which were not etiologically related to vitamin deficiency, 2 with pellagra and 3 with evidence of multiple vitamin deficiency. A careful history in regard to diet was elicited from each person, attention being especially directed to the intake of vitamin C. In 3 cases in which a marked deficiency of ascorbic acid was found at the original examination, a second test was carried out subsequent to a period of treatment with

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vitamin C. No patient with fever or an acute infectious process was included in this study.

METHOD

A specimen of blood and one of urine were collected from the patient in the fasting state. Afterward 600 mg. of ascorbic acid [1] was administered by mouth. Specimens of blood and urine were obtained at the end of one, three and six hours. Each specimen of urine included the entire amount voided after the time of the previous collection. Similarly, all urine passed from the sixth to the twelfth and from the twelfth to the twenty-fourth hour after the test dose was saved for examination. In a few instances a twenty-four hour specimen was collected the day prior to the administration of the test dose of ascorbic acid for comparison of findings. The urine was kept in dark, tightly stoppered bottles on ice and was acidified with glacial acetic acid (approximately 10 per cent by volume), these procedures having been shown to retard the oxidation of vitamin C. Day specimens were analyzed at once in most instances, always within two hours. One cubic centimeter of acidified urine, diluted with 10 cc. of distilled water, was titrated against a solution of 2,6-dichlorophenolindophenol of such a concentration that 1 cc. of the dye was equivalent to 0.02 mg. of ascorbic acid. The quantity of urine in each of the specimens was measured, and the amount of ascorbic acid present was calculated. When the urine was highly colored, it was often necessary to dilute it with more than 10 cc. of distilled water in order to obtain a definite end point. When a large amount of vitamin C was present in the specimen, dilution was first made, after which 1 cc. of the diluted specimen was used in titration with the dye.

As a result of special observations we found that there was only a slight diminution in the amount of vitamin C in the urine if analysis was delayed for one or two hours when it had been collected as described, but after twenty-four hours the decrease at times amounted to 20 per cent or more. Similar findings have been reported by Abbasy, Harris, Ray and Marrack [2] and by Wright.[3]

The amount of reduced ascorbic acid in the blood plasma was determined by the method of Farmer and Abt.[4] Ten cubic centimeters of blood was collected in a tube containing oxalate and centrifuged immediately. Two cubic centimeters of plasma was transferred to another tube, to which was added 4 cc. of distilled water and 4 cc. of a 5 per cent solution of metaphosphoric acid. After further centrifugation, 2 cc. of the supernatant fluid was titrated against a solution of 2,6-dichlorophenolindophenol of such a concentration that 1 cc. of the dye was equivalent to 0.01 mg. of ascorbic acid. The solutions of the dye (2,6-dichlorophenolindophenol) were prepared from tablets, each of which was equal to 1 mg. of ascorbic acid. These were checked against freshly prepared solutions of ascorbic acid of known concentration and found to be accurate within the limits of experimental error of this method.

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1. The ascorbic acid used was supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.

2. Abbasy, M. A.; Harris, L. J.; Ray, S. N., and Marrack, J. R.: Diagnosis of Vitamin C Subnutrition by Urinalysis, Lancet **2**:1399, 1935.

3. Wright, I.: The Present Status of the Clinical Use of Cevitamic Acid, Am. J. M. Sc. **192**:719, 1936.

4. Farmer, C. J., and Abt, A. F.: Determination of Reduced Ascorbic Acid in Small Amounts of Blood, Proc. Soc. Exper. Biol. & Med. **34**:146, 1936.

A microburet reading to 0.01 cc. was used in all titrations, the dye being titrated into the fluid being tested. The latter was placed in a white evaporating dish and a blue light used to facilitate determination of the end point, which was considered to be the first pink color lasting thirty seconds. All titrations were completed within two minutes. A distilled water blank value was determined, this value being subtracted from the final buret reading. Each titration was done in duplicate by each of two observers, and the average of these values was used in calculating the content of ascorbic acid in the specimen.

TABLE 1.—*Vitamin C Content of the Blood and Urine*

Test No.	Case No.	Diagnosis	Dietary History of Vitamin C	Control, 24 Hour Output in Urine, Mg.	Blood (Fasting), Mg. per 100 Cc.	Vitamin C Content After Administration of 600 Mg. of Ascorbic Acid: Blood, Highest Concentration, Mg. per 100 Cc.	6 Hour Output in Urine, Mg.	Percentage of 24 Hour Output in Urine	24 Hour Output in Urine, Mg.	Percentage of Test Dose Excreted
1	1	Hypovitaminosis	Very poor	.....	0.05	0.31	0.95	88	1.08	0.2
2	2	Hypovitaminosis	Very poor	.....	0.05	0.12	0.62	55	1.12	0.2
3	3	Hypovitaminosis	Very poor	.....	0.06	0.20	0.49	17	2.86	0.5
4	4	Pellagra	Very poor	1.820	0.09	0.50	2.60	77	3.38	0.6
5	5	Rheumatic heart disease	Very poor	.....	0.07	0.24	0.71	20	3.54	0.6
6	6	Epilepsy	Poor ?	.....	0.21	0.86	3.07	75	4.06	0.7
7	7	Syphilitic heart disease	Very poor	.....	0.17	0.64	0.33	7	4.45	0.7
8	8	Psychoneurosis	Poor	.....	0.04	0.84	2.24	40	5.61	0.9
9	9	Psychoneurosis	Poor	10.670	0.19	0.47	2.80	41	6.87	1.1
10	10	Psychoneurosis	Fair	.....	0.19	1.05	3.43	43	7.87	1.3
11	11	Normal	Fair ?	9.003	0.17	0.76	3.11	35	8.87	1.5
12	12	Psychoneurosis	Poor	6.150	0.21	1.15	3.97	41	9.55	1.6
13	13	Hookworm	Poor	9.240	0.52	1.71	3.46	36	9.63	1.6
14	14	Arteriosclerosis; allergy	1,050 mg. in 21 days; poor previously	.....	0.34	1.55	4.99	35	14.12	2.3
15	15	Mild pellagra	Fair	.....	0.74	2.72	26.93	..	....	...
16	16	Psychoneurosis	Fair	.....	1.22	1.74	49.50	..	....	...
17	2	Hypovitaminosis; after treatment	3,900 mg. in 13 days	46.640	0.98	2.18	50.19	70	70.84	12.0
18	17	Psychoneurosis	Fair	.....	0.43	2.32	70.49	85	82.70	13.7
19	18	Diabetes	Good	.....	0.80	2.48	81.57	74	109.53	18.0
20	19	Chronic bacillary dysentery	Very good	.....	0.82	2.99	48.59	41	116.31	19.0
21	20	Normal	Good	12.190	0.65	2.00	103.05	75	137.09	23.0
22	4	Pellagra; after treatment	4,500 mg. in 15 days	.....	1.61	2.48	136.05	75	179.70	30.0
23	21	Rheumatoid arthritis	Excellent	.....	1.74	2.16	209.02	91	228.34	38.0
24	22	Normal	Excellent	17.800	1.38	2.97	109.73	45	240.40	40.0
25	3	Hypovitaminosis; after treatment	3,500 mg. in 9 days	.....	1.98	2.60	180.16	62	291.15	48.5

RESULTS

A number of pertinent findings made in the 25 tests which were performed are given in table 1. The results are listed in ascending order according to the amount of ascorbic acid excreted in the urine in twenty-four hours after the administration of the test dose. It may be seen that, in general, the better the dietary history in regard to vitamin C, the greater the output in the urine after the test dose. The amount of ascorbic acid excreted in six hours was calculated as well as the output in twenty-four hours, and the results were found to be

closely parallel. This observation will be discussed in detail later. The amount of reduced ascorbic acid in the blood during fasting likewise showed a close correlation with the previous dietary intake and also with the quantity of vitamin C excreted in the urine. The concentration of ascorbic acid in the blood reached higher levels after the administration of the test dose when the amount present during fasting was high. Little information regarding saturation of the tissues with vitamin C was obtained from examining the urine for twenty-four hours prior to the giving of a test dose of the vitamin except in 2 instances, 1 patient (case 4) showing extreme deficiency and another (case 2, test 17) a normal condition.

On the basis of the following considerations, the first 14 tests have been considered as indicative of vitamin C deficiency and the last 11 tests as indicative of a fairly normal state of nutrition. Abbasy, Harris, Ray and Marrack [2] have shown that for the normal person the minimal daily excretion of vitamin C in the urine in twenty-four hours is 13 mg. and that after the administration of a test dose of 700 mg. there is an excretion of 40 to 50 mg. in the subsequent twenty-four hours. The first 14 tests, that is, those designated as indicating deficiency, fail to meet these criteria; while the last 9 tests, considered as indicating a normal condition, satisfy these requirements. Two patients (cases 15 and 16) were given only six hour tests but were placed in the group of normal patients for reasons which will be discussed later. Van Eekelen [5] has stated that when vitamin C is being administered daily in amounts varying from 250 to 400 mg., as saturation of the tissues is reached there is a definite rise in the urinary output of vitamin C (above 30 mg.). Even with a single large dose of ascorbic acid, a urinary excretion of 70 mg. or more in twenty-four hours, as shown in tests 17 through 25, seems significant of near saturation.

The last column in table 1 indicates the percentage of the test dose excreted in the twenty-four hours following its administration. Hawley and Stephens [6] found that saturated subjects excreted 40 to 100 per cent of an oral test dose of 100 to 200 mg. in this period. Wright [3] stated that about 30 per cent of a test dose of 500 to 1,000 mg. should be excreted in twenty-four hours and that an output of less than 20 per cent indicates suboptimal storage of vitamin C. Youmans [7] concluded that excretion of 30 per cent or more of a test dose of 600 mg. is the lower limit of saturation. Using these criteria, the last 5, and

5. Van Eekelen, M.: On the Amount of Ascorbic Acid in Blood and Urine: Daily Human Requirements for Ascorbic Acid, Biochem. J. **30**:2291, 1936.

6. Hawley, E. E., and Stephens, D. J.: Rate of Urinary Excretion of Test Doses of Ascorbic Acid, Proc. Soc. Exper. Biol. & Med. **34**:854, 1936.

7. Youmans, J. B.; Corlette, M. B.; Akeroyd, J. H., and Frank, H.: Studies of Vitamin C Excretion and Saturation, Am. J. M. Sc. **191**:319, 1936.

possibly the last 7, tests may be considered to indicate saturation and the preceding 2 near saturation.

Detailed Study of Urinary Excretion.—Examination of the specimen of urine obtained from the patient in the fasting state gave little and often misleading information. The content of ascorbic acid varied considerably both in the normal and in the deficient persons (table 2), and there was marked overlapping of findings. This confirms the view of a number of investigators that examination of a single specimen of urine is valueless.

TABLE 2.—*Ascorbic Acid in the Urine After a Test Dose of Ascorbic Acid* *

		Output of Ascorbic Acid, Mg.					
	Test No.	During Fasting	1 Hr.	1-3 Hr.	3-6 Hr.	6-12 Hr.	12-24 Hr.
Deficient persons	1	0.41	0.05	0.37	0.53	†	0.13
	2	0.14	0.25	0.16	0.21	0.24	0.26
	3	0.21	0.37	0	0.12	†	2.38
	4	0.46	0.30	0.78	1.52	†	0.78
	5	0.07	0.07	0.07	0.57	†	2.83
	6	2.27	0.43	1.14	1.50	†	0.99
	7	0.18	0.08	0.02	0.24	1.67	2.45
	8	0.63	0.29	0.67	1.29	1.03	2.34
	9	0.81	0.37	0.88	1.55	1.64	2.42
	10	0.41	0.33	1.02	2.06	1.11	3.33
	11	0.25	0.35	0.73	2.02	3.03	2.73
	12	0.17	0.47	1.10	2.42	3.19	2.40
	13	1.54	1.27	1.31	0.88	1.92	4.25
	14	0.18	0.32	1.27	3.40	6.61	2.52
Normal persons	15	0.07	0.22	12.29	14.42	‡	‡
	16	9.63	5.57	16.80	27.12	‡	‡
	17	†	2.14	20.64	27.40	12.84	7.81
	18	0.32	0.36	11.47	58.65	7.47	4.75
	19	0.06	0.79	16.49	64.31	20.17	7.76
	20	0.36	1.36	3.21	44.03	†	67.72
	21	1.07	0.53	18.24	84.28	28.52	5.52
	22	0.44	0.74	94.90	40.41	41.80	1.84
	23	1.94	5.45	112.07	91.50	11.41	7.90
	24	0.66	0.97	54.94	53.82	116.48	14.19
	25	1.72	3.14	54.27	122.75	50.24	64.75

* The test dose consisted of 600 mg. of ascorbic acid.
† Included in the twelve to twenty-four hour specimen.
‡ No specimen was collected.

One hour after the administration of the test dose, all but 2 of the group of normal persons showed an increase in the amount of ascorbic acid in the urine, but in only 3 instances was it of significant degree (to 1 mg. or more). For the group of deficient persons there was a rise in only 4 tests, this increase amounting in each case to less than 0.3 mg. The urine which was collected between the first and the third hour after the administration of the test dose showed a marked increase in the quantity of ascorbic acid excreted by all normal persons, the amount varying from 3.2 to 112 mg. For the subjects who showed deficiency, there was no increase in the output of vitamin C in this period, or else the rise amounted to less than 1 mg. In the specimen collected between the third and the sixth hour after the test dose, the

quantity of ascorbic acid eliminated by normal persons ranged from 14.4 to 122.7 mg.; for those who were deficient the quantity ranged from 0.12 to 3.4 mg. At the end of twelve hours the excretion of vitamin C continued to be increased for the normal persons but at a slower rate, and at the end of twenty-four hours the excretion had decreased almost to the level noted before the test dose was given.

For the subjects who were normal in regard to vitamin C, the rate of excretion per hour was greatest between the first and the third hour in 6 instances, varying from 1.6 to 56 mg., and between the third and the sixth hour in 5 instances, varying from 4.8 to 40.9 mg. The amount of ascorbic acid per cubic centimeter of urine was calculated throughout our investigation but was found to be an unreliable measure of the actual excretion, owing to wide variations in dilution and concentration; hence the total output in the urine during a given period should always be determined.

In summary, when vitamin C nutrition is normal, the response to 600 mg. of ascorbic acid given orally is a marked rise in urinary excretion, beginning at the end of the first hour and reaching a peak some time between the first and the sixth hour, followed by a gradual decline, approaching the original level at the end of twenty-four hours. When the vitamin C stores of the body are deficient, there is no rise in the output of vitamin C in the urine, or an insignificant one, after the test dose.

PROPOSED SIX HOUR URINARY EXCRETION TEST FOR SATURATION

Since the greatest increase in excretion of ascorbic acid in the urine occurred during the first six hours after the administration of 600 mg. of this substance, the total output in this period was calculated and compared with the amount excreted in twenty-four hours. In chart 1 the findings are shown graphically, the solid columns representing the six hour and the total columns the twenty-four hour excretions. It may be seen that when the excretion during the twenty-four hour period was high or low the same was true regarding the six hour period. In the group of normal persons from 41 to 91 per cent (average 61 per cent) of the total amount of vitamin C excreted in twenty-four hours was excreted in the first six hours (table 1); in the group of deficient persons from 7 to 88 per cent (average 44 per cent) was excreted. Hawley and Stephens [6] reported similar findings, using a test dose of 100 to 200 mg. given by mouth. They found that saturated subjects excreted 55 per cent and depleted ones 47 per cent of the twenty-four hour output in the first six hours. In our series the actual amount of vitamin C eliminated in six hours after the administration of the test dose varied from 48.5 to 209 mg. for the normal persons and from

0.3 to 4.9 mg. for the depleted persons. When over 20 per cent of the amount of vitamin C administered was excreted in twenty-four hours (e. g., when the tissues were nearly saturated), the six hour output was above 100 mg. In 2 instances only a six hour test was performed. One patient (case 16) excreted 49.5 mg. in this period; the other (case 15), who had pellagra, excreted 27 mg. The findings in each of these instances have been considered to represent normal nutrition. An output of 49.5 mg. is comparable to that found in several tests of normal

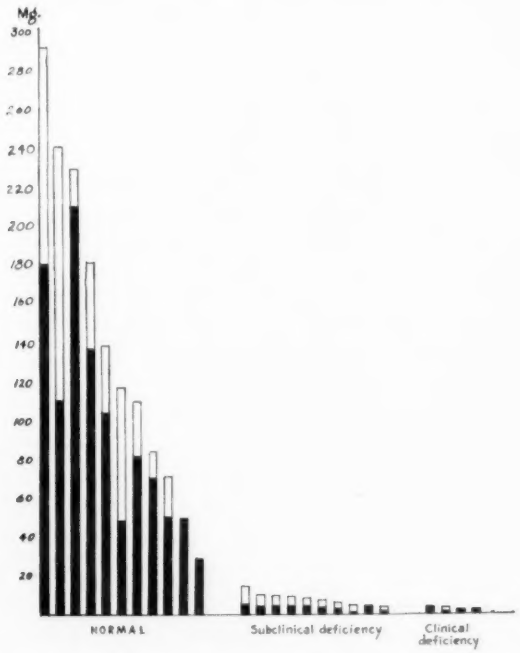

Chart 1.—Urinary excretion of vitamin C after the administration of a test dose of 600 mg. of ascorbic acid. The black columns indicate the six hour output, and the white columns indicate the twenty-four hour output.

persons. An excretion of 27 mg. may indicate slight subnutrition, but examination of the blood in this case showed no evidence of deficiency.

In view of these findings, it seems that as much information can be obtained by examining the urine for the content of ascorbic acid excreted in six hours as by examining that excreted in twenty-four hours after the administration of a test dose of this substance. To test the vitamin C nutrition, 600 mg. of ascorbic acid may be given

by mouth and the urine collected for the subsequent six hours. If 50 mg. or more is excreted, the person may be considered normal in regard to the ascorbic acid content of the body; while if over 100 mg. is excreted, partial or actual saturation of the tissues is indicated. Excretion of less than 50 mg. may be associated with depletion of the vitamin C stores of the body.

Harris and Abbasy [8] have recently proposed a simplified procedure to determine the state of vitamin C nutrition, in which the output of ascorbic acid is measured between the fourth and the seventh hour after the administration of a test dose of this substance. Our findings for a comparable period, between the third and the sixth hour, showed an output for the normal persons of from 27.4 to 122.7 mg. (table 2), the amount excreted averaging 44 per cent of the total twenty-four hour excretion. By the depleted persons from 0.1 to 3.4 mg. was excreted, the output averaging 23 per cent of the twenty-four hour excretion. Examination of the urine for this short interval after the test dose, during which the maximum increase in the excretion of vitamin C occurs, gave considerable information regarding the state of vitamin C nutrition.

ASCORBIC ACID IN THE BLOOD

In the Fasting State.—In our series of 25 tests the level of reduced ascorbic acid in the blood varied from 0.04 to 1.98 mg. per hundred cubic centimeters (table 1). For the group considered normal according to findings obtained on examination of the urine, from 0.43 to 1.98 mg., with an average of 1.11 mg., of ascorbic acid was present per hundred cubic centimeters of blood; for the group considered deficient, from 0.4 to 0.52 mg., with an average of 0.17 mg., per hundred cubic centimeters. Six subjects showed less than 0.1 mg. per hundred cubic centimeters, 4 of them exhibiting clinical evidence of vitamin deficiency. Normal blood values during fasting range from 0.65 to 2 mg. per hundred cubic centimeters, according to various observers, figures above 1.3 mg. being indicative of saturation. [9] Only 1 of the group

8. Harris, L. J., and Abbasy, M. A.: A Simplified Procedure for the Vitamin C Urine Test, Lancet **2**:1429, 1937.

9. (*a*) Wright I. S.; Lilienfeld, A., and MacLenathen, E.: Determination of Vitamin C Saturation: A Five Hour Test After an Intravenous Test Dose, Arch. Int. Med. **60**:264 (Aug.) 1937. (*b*) Pijoan, M., and Klemperer, F.: Determination of Blood Ascorbic Acid, J. Clin. Investigation **16**:443, 1937. (*c*) Abt, A. F.; Farmer, C. J., and Epstein, I. M.: Normal Cevitamic Acid Determinations in Blood Plasma and Their Relationship to Capillary Resistance, J. Pediat. **8**:1, 1936. (*d*) Greenberg, L. D.; Rinehart, J. F., and Phatak, N. M.: Studies on Reduced Ascorbic Acid Content of Blood Plasma, Proc. Soc. Exper. Biol. & Med. **35**:135, 1936. (*e*) Van Eekelen.[5]

of normal persons showed less than 0.65 mg., presenting a value of 0.43 mg. This person's response to a test dose of vitamin C was normal as far as urinary excretion was concerned. The low value may have been due to a reduced intake of this vitamin for a day or two prior to the test, the diet previously having been adequate. This one finding indicates that occasionally a single determination of the ascorbic acid in the blood may lead to fallacious interpretation. Of the 4 persons with blood values above 1.3 mg. per hundred cubic centimeters, which is considered the level of saturation, all excreted 30 per cent or more of the test dose in the urine in twenty-four hours (table 1) and 109 mg. or more in six hours. The subjects showing values between 0.65 and 1.3 mg. per hundred cubic centimeters, which is considered normal, excreted 12 to 23 per cent of the test dose in the urine in twenty-four hours and 48.5 mg. or more in six hours. The patients with values of less than 0.65 mg. per hundred cubic centimeters had an output of 0.2 to 2.3 per cent of the test dose in the urine in twenty-four hours and an output of less than 5 mg. in six hours. There was 1 exception; the person previously mentioned who showed a blood level of 0.43 mg. per hundred cubic centimeters during fasting excreted 13.7 per cent of the test dose in twenty-four hours and 70 mg. in six hours. These figures show the close correlation between urinary and blood findings as indicative of normal or deficient vitamin C nutrition.

After the Administration of 600 Mg. of Ascorbic Acid as a Test Dose.—The blood was examined for the content of reduced ascorbic acid one, three and six hours after the oral administration of 600 mg. of ascorbic acid (chart 2). At the end of one hour there was a rise in the concentration of ascorbic acid; this rise persisted or reached a peak at the end of three hours. After six hours had elapsed there was usually a slight fall in the amount of vitamin C in the blood. The curves resembled those for a dextrose tolerance test, as has been suggested by Greenberg, Rinehart and Phatak.[9d] These investigators obtained a maximum increase two to four and one-half hours after giving 6 ounces (177 cc.) of orange juice. Taylor, Chase and Faulkner [10] administered 1 Gm. of ascorbic acid and found that normal persons showed a rise in the concentration in the blood which reached a peak in one hour and subsided in five hours. In 1 case of scurvy the rise was delayed, reaching a maximum at three hours and remaining high for two hours longer. In our series, the group of normal persons (11 tests) showed a rise to a maximum of 1.7 to 2.9 mg. of ascorbic acid per hundred cubic centimeters of blood. In all but 1 instance a height of 2 mg. or more was attained. For the group of deficient persons (14 tests) the highest

10. Taylor, F. H. L.; Chase, D., and Faulkner, J. M.: Estimation of Reduced Ascorbic Acid in Blood Serum and Plasma. Biochem. J. **30**:1119, 1936.

concentration varied from 1.2 to 1.7 mg. of ascorbic acid per hundred cubic centimeters, a rise above 1.1 mg. occurring in only 2 tests. In all but 3 instances the maximum concentration was reached one to three hours after the test dose was given. A delayed rise may be due to slow absorption from the gastrointestinal tract or to diminished excretion by the kidneys due to renal damage. One person who showed this type of curve had chronic bacillary dysentery, 1 had generalized arteriosclerosis with evidence of diminished renal function and a third was a normal adult in good health. In patients in whom disease of the gastrointestinal tract is interfering with absorption, vitamin C nutrition may be tested by administering ascorbic acid intravenously.

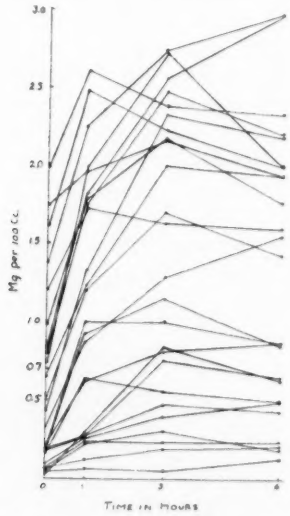

Chart 2.—The reduced ascorbic acid content of the blood after a test dose of 600 mg. of ascorbic acid.

PROPOSED TEST OF THE BLOOD FOR VITAMIN C NUTRITION

The state of saturation of the tissues may be determined by examining the blood during fasting and one and three hours after the administration of 600 mg. of ascorbic acid. An original level of reduced ascorbic acid of over 0.7 mg. per hundred cubic centimeters, reaching 2 mg. or more after the test dose, may be considered indicative of normal vitamin C nutrition. A value of over 1.3 mg. per hundred cubic centimeters for the blood during fasting indicates tissue saturation. If the amount of vitamin C in the blood during fasting is less than 0.7 mg.

and if it fails to rise to 2 mg. or more at the end of three hours after the test dose, vitamin C deficiency is present.

THE RENAL THRESHOLD OF VITAMIN C

The findings obtained on examination of the blood and of the urine showed a close correlation. When the level of ascorbic acid in the blood during fasting was high or when a high level was reached and

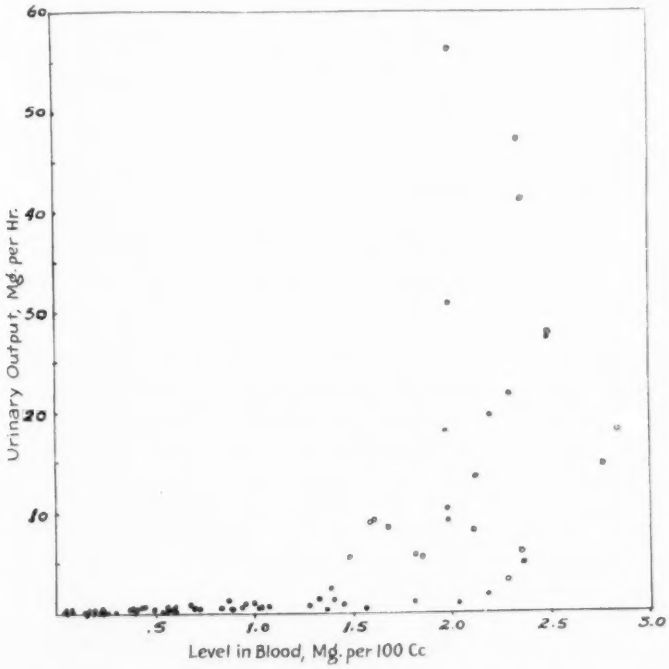

Chart 3.—The relation between the amount of ascorbic acid in the blood and the amount excreted in the urine.

maintained after the administration of a test dose, a large amount was excreted in the urine; when the quantity in the blood during fasting was low and when the rise was small, the urinary excretion was minimal. In chart 3 the amount of vitamin C excreted per hour in the urine is plotted against the concentration of ascorbic acid in the blood during the same period. The latter figure was obtained by averaging the concentration in the blood at the beginning and at the end of the particular period of urinary excretion. It can be seen that little vitamin C was

excreted by the kidneys until the level in the blood reached approximately 1.4 mg. per hundred cubic centimeters, at which time an increase in the excretion of vitamin C occurred. Van Eekelen [5] has stated that when the level of ascorbic acid in the blood is greater than 1.3 mg. per hundred cubic centimeters, the excretion in the urine is increased. Faulkner and Taylor [11] have reported a renal threshold of vitamin C in the neighborhood of 1.4 mg. of reduced ascorbic acid per hundred cubic centimeters of blood.

STUDIES OF THREE PATIENTS WITH VITAMIN DEFICIENCY

Three patients who showed clinical signs of vitamin deficiency were studied at the time of admission to the hospital and after a period of treatment with vitamin C (table 1, tests 2, 3, 4, 17, 22 and 25). One of the patients had pellagra, with both cutaneous and gastrointestinal manifestations. Her diet had consisted of dried beans, rice, bread and coffee, with inclusion of meat and canned vegetables only once or twice weekly and citrus fruits about once a month. A second patient was originally considered as having a gastric neurosis, but it was subsequently shown that she was extremely deficient in vitamin C. For two months her diet had been extremely meager, containing small amounts of lean meat, rice and a few cooked vegetables, with no citrus fruits, tomatoes or cabbage. The third patient exhibited stomatitis, esophagitis, proctitis, vaginitis and evidence of loss of weight and dehydration. Her diet had been deficient for several months both in quantity and in quality, and she had never eaten citrus fruits or tomatoes to any extent. After the state of vitamin C nutrition had been tested, each of these patients was given 300 to 400 mg. of ascorbic acid daily, and at the end of nine to fifteen days a second test was performed.

The results of the primary and subsequent tests are shown in chart 4. At the time of the original examination, after the administration of 600 mg. of ascorbic acid, the urinary excretion was 1.1, 2.9 and 3.4 mg., respectively, of vitamin C in twenty-four hours, 0.5, 0.6 and 2.6 mg., respectively, being excreted in six hours. In other words, practically no ascorbic acid was excreted in the urine, as these small values may have been due to reduction of the dye (2,6-dichlorophenolindophenol) by other substances. The blood at this time showed during fasting 0.05, 0.06 and 0.09 mg., respectively, of ascorbic acid per hundred cubic centimeters. After the test dose the concentration rose to a peak of 0.12, 0.2 and 0.5 mg., respectively, per hundred cubic centimeters. After the period of vitamin C therapy and after the test dose the urinary excretion was 70.8, 179.7 and 291.1 mg., respectively, in twenty-four

11. Faulkner, J. M., and Taylor, F. H. L.: Observations on the Renal Threshold for Ascorbic Acid in Man, J. Clin. Investigation **17**:69, 1938.

hours and 50.2, 136 and 180.2 mg., respectively, in six hours. The level of reduced ascorbic acid in the blood during fasting measured 0.98, 1.61 and 1.98 mg., respectively, per hundred cubic centimeters, rising after the test dose to 2.18, 2.48 and 2.6 mg., respectively, per hundred cubic centimeters. In other words, the vitamin C nutrition was normal, as judged by the examination of the urine and of the blood. From a clinical standpoint, all 3 patients were markedly improved. The gastrointestinal symptoms had cleared up in 1 case, the stomatitis, proctitis and vaginitis had disappeared in 1 case and the lesions of pellagra had nearly disappeared in the third case. The third patient was the only one to receive treatment other than vitamin C in addition to the ordinary hospital diet. She was also given large amounts of brewers' yeast daily.

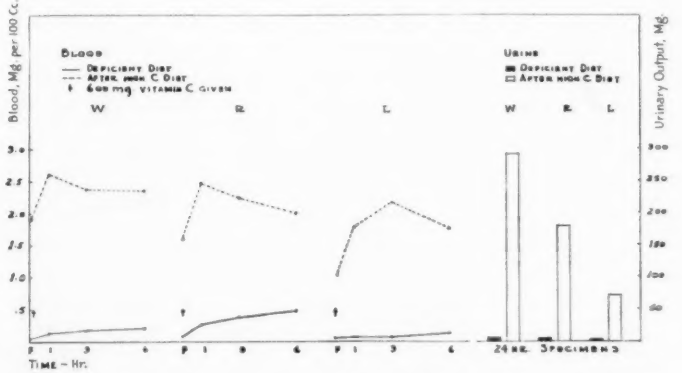

Chart 4.—The ascorbic acid content of the blood and urine in deficiency states (3 cases) when the original diet was being taken and after a high intake of vitamin C.

Of the 2 patients in this series who had pellagra, 1 showed marked deficiency of vitamin C, as already described (table 1, case 4); the other, for whom only a six hour test of blood and urine was performed, revealed findings at the low limit of normal (table 1, case 15). It seems likely that when a person exhibits deficiency of one vitamin, there may be deficiency of other vitamins as well. States of multiple vitamin deficiency have been recognized with increasing frequency in recent years. A further study of the state of vitamin C nutrition in patients with pellagra is being undertaken. It is conceivable that some of the symptoms of this disease are due to lack of substances other than vitamin B_2 (or G), the pellagra-preventive factor.

FREQUENCY OF VITAMIN C DEFICIENCY

Deficiency of ascorbic acid is a frequent finding in routine examination of patients in clinics and hospitals, as shown by Harris, Abbasy, Yudkin and Kelly.[12] In this small series of 22 patients, of whom 17 were apparently normal clinically in regard to vitamin C nutrition, 14 showed evidence of deficiency with special testing. Numerous vague complaints, such as fatigue, anorexia and indigestion, may be related to deficiency of this nutritive factor. More definite disorders, such as stomatitis, vaginitis and proctitis, may be caused by an insufficient amount of vitamin C in the tissues of the body. On the other hand, in view of the prevalence of subclinical vitamin C deficiency, caution should be used before attributing to ascorbic acid the role of an etiologic factor in any pathologic state. A depletion of the vitamin C content of the tissues may be only a concomitant finding or a result rather than a cause of the disease which is being studied.

COMMENT

The results of this study and the findings of Harris and Abbasy,[8] previously mentioned, indicate that it is not necessary to measure the excretion of ascorbic acid for twenty-four hours after giving a test dose to determine the state of vitamin C nutrition. Since this investigation was started, a short test has been reported by Wright and his co-workers,[9a] consisting of a study of urinary excretion for five hours after the administration of 1,000 mg. of ascorbic acid intravenously. The excretion of 400 mg. in this period was considered to indicate normal nutrition. Ralli, Friedman and Kaslow [13] have proposed the use of a three hour test of urinary excretion after the administration of 100 mg. of vitamin C by vein, having found that normal persons excrete 40 per cent and depleted subjects 11 per cent of the injected vitamin in three hours. The principle in each of these procedures is the same, the variants being the amount of vitamin C used as a test dose, the method of administration and the number of hours during which urine is collected. A dose of 600 mg. was chosen for our study because it was large enough to minimize the effect of reducing substances other than vitamin C in the urine and also to diminish the significance of the inherent error in the determination of the end point. Similar amounts

12. Harris, L. J.; Abbasy, M. A.; Yudkin, J., and Kelly, S.: Vitamins in Human Nutrition: Vitamin C Reserves of Subjects of Voluntary Hospital Class, Lancet **1**:1488, 1936.

13. Ralli, E. P.; Friedman, G. J., and Kaslow, M.: Excretory Test for Vitamin C Deficiency and Subnutrition, Proc. Soc. Exper. Biol. & Med. **36**:52, 1937.

have been used in previous investigations, and an opportunity was afforded for comparison of results. The oral route is the simplest method of administration and is satisfactory in most instances, although occasionally findings may be inaccurate because of poor intestinal absorption. Van Eekelen and Heinemann [14] have suggested that intravenous administration or the use of large doses, over 300 mg., may simulate saturation. Erroneous conclusions may result if ascorbic acid is spilled into the urine, insufficient time being allowed for absorption by the tissues. Wright [9a] has stated that in order to avoid the danger of irregular intestinal absorption, ascorbic acid should be given by vein. In all examinations of the urine the presence of reducing substances other than vitamin C is a potential source of error. Van Eekelen and Heinemann [14] have indicated that this is especially true when the diet is high in protein or when diabetes is present. They have advocated removal of these reducing substances by precipitation with mercuric acetate. King,[15] however, has criticized this procedure because it introduces new sources of error. In choosing a method to determine the vitamin C nutrition and in evaluating the results, all these facts should be kept in mind. It is our opinion that for routine clinical use the administration of an oral test dose of ascorbic acid with examination of the urine excreted in a period of three or six hours is a satisfactory procedure.

Examination of the blood is free from much of the aforementioned criticism, and a saturation test dependent on estimation of the content of reduced ascorbic acid in the blood may prove to be more reliable than tests of the urine. Such a procedure has been suggested as a result of this study.

With the availability of methods which require only a few hours for their performance and which are applicable to ambulatory patients, an opportunity is afforded for studying large groups of persons, as a result of which the role of vitamin C in a number of pathologic states may be clarified.

SUMMARY

The state of vitamin C nutrition may be determined by measuring the excretion of ascorbic acid in the urine for six hours after the administration of 600 mg. of this substance. An alternative procedure consists in the determination of the amount of reduced ascorbic acid in the blood during fasting and at the end of one hour and of three

14. Van Eekelen, M., and Heinemann, M.: Critical Remarks on the Determination of Urinary Excretion of Ascorbic Acid, J. Clin. Investigation **17**:293, 1938.

15. King, C. G.: Vitamin C, Ascorbic Acid, Physiol. Rev. **16**:238, 1936.

hours after the administration of a similar test dose. Criteria of normal vitamin C nutrition, of saturation and of depletion of the tissues are enumerated for each of these tests.

There is a definite relation between the level of reduced ascorbic acid in the blood and the amount of this substance excreted by the kidneys; when the former exceeds 1.4 mg. per hundred cubic centimeters, urinary excretion increases.

Mild vitamin C deficiency is extremely prevalent, and too much importance should not be attached to depletion of the ascorbic acid content of the body in any disease.

INTRAPERITONEAL PRESSURE DURING TREATMENT WITH ARTIFICIAL PNEUMOPERITONEUM

A CLINICAL STUDY

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The purpose of this paper is to present a series of observations on the intraperitoneal pressure that was recorded during the course of pneumoperitoneum treatment of 91 patients with pulmonary tuberculosis. For measuring the intraperitoneal pressure the manometer of an ordinary pneumothorax apparatus, graduated in half centimeters, was used. The patient was in the supine position except when the needle was introduced by the subdiaphragmatic route, in which case he was lying on his side. In the overwhelming majority of instances the site of insertion of the needle was 3 fingerbreadths below and to the left of the umbilicus. When the subdiaphragmatic route was used the needle was inserted slightly above the costal margin. All manometer readings were taken during quiet respiration.

The initial treatment was always given by the subumbilical route. The intraperitoneal pressure at this point is, as a rule, neutral (atmospheric). There were only 7 patients for whom the initial reading was slightly negative, or subatmospheric. This can be explained by the fact that in rare instances the subdiaphragmatic pressure is transmitted as far as the subumbilical region. In another group of patients that I treated with pneumoperitoneum by the subdiaphragmatic route I found that under normal conditions the intraperitoneal pressure was negative in that area. The cause is the transmission of negative pressure from the corresponding pleural cavity.

An illustration of the changes in the intraperitoneal pressure following the injection of a gradually increasing amount of air is presented in the accompanying table. The graphs show that the same amount of air may elicit different degrees of rise in pressure in different persons. The factors that are responsible for this are: (1) the variable tonicity and integrity of the abdominal wall, including the diaphragm, (2) the variable size of the abdominal cavity, (3) the variable status of the lung and pleura and (4) the presence or absence of peritoneal adhesions. The abdominal wall is likely to relax after the injection of air, to

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counteract the increased intraperitoneal pressure. This reflex accommodation on the part of the muscles of the abdominal wall has been recognized in many instances by the fact that there is a considerable drop in the manometer reading two or three minutes after the injection. Chart 1 illustrates this point. A steep, rapidly rising curve signifies a case in which readings were taken directly after the injection and the injections were continued immediately afterward. In instances in

Maximum Direct Intraperitoneal Pressure

	Number of Treatments															
Manometer Readings	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
After injection of 500 cc. of air..	11	13	18	17	17	18	16	15	16	18	18	18	15	16	14	16	13
After injection of 1,000 cc. of air..	6	14	20	18	21	18	22	19	22	21	22	20	16	16	20	17	18
Prior to periodic refills.....	..	8	16	16	14	17	13	14	11	19	20	14	13	10	14	13	12

	Number of Treatments															
Manometer Readings	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
After injection of 500 cc. of air..	18	14	16	18	19	13	13	14	13	14	16	17	18	13	20	14
After injection of 1,000 cc. of air..	21	18	20	22	20	16	17	13	16	20	22	22	24	20	24	24
Prior to periodic refills.....	17	10	14	15	15	18	14	12	15	16	17	17	20	15	15	20

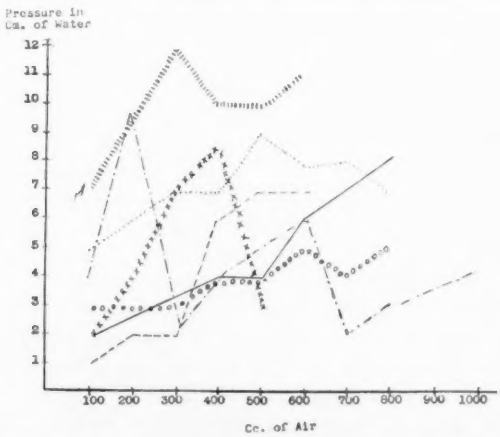

Chart 1.—Changes in the intraperitoneal pressure after the injection of gradually increased amounts of air at the first treatment. Each curve indicates data for a different patient.

which some time was permitted to elapse between the reading of the manometer and the injection of air, there was a drop in pressure in spite of the additional amount of injected air. In 1 instance the pressure decreased by 8 cm. of water. One must therefore consider two kinds of intraperitoneal pressure; (1) the direct pressure, observed immedi-

ately after the injection of air, and (2) the indirect or delayed pressure that registers after abdominal accommodation has occurred.

The difference between direct and indirect intraperitoneal pressure is noticeable throughout the course of treatment. It is, however, less marked when pneumoperitoneum is well established than at the beginning of the treatment. I have made no attempt to determine the time necessary for the return of increased intraperitoneal pressure to normal. The greatest drop in pressure in a two minute period was 10 cm. of water; it occurred after the injection of 800 cc. of air at the fourth treatment. In no instance have I seen the pressure drop below 2 cm. in two minutes. On the other hand, I have observed a return of the intraperitoneal pressure to the atmospheric level in a week, although it had been as much as + 5, + 9, + 11 and even + 14 cm. at the completion of a previous injection a week before.

In contrast to this observation, I have had patients for whom a persistently positive manometer reading was noted at weekly intervals after the first injection throughout the course of treatment. There were 12 patients for whom positive pressure was noted only occasionally when weekly treatments were given. This group of patients included 6 who prior to the establishment of pneumoperitoneum had undergone surgical paralysis of the phrenic nerve (this operation may add considerably to the abdominal capacity) and 2 patients in whom flabbiness of the anterior abdominal wall allowed considerable distention after the injection of air. I have calculated that for 74 patients in whom a persistent positive intraperitoneal pressure was established an average of approximately 5,300 cc. of air in six treatments was required to attain it. The average pressure at the sixth treatment in these cases was 3.8 cm. of water.

The appearance of a positive intraperitoneal pressure at the time of periodic measurements does not necessarily mean the establishment of a constant positive pressure. I have seen a number of patients for whom positive readings were recorded at weekly refills prior to the injection of air on one or on several occasions but for whom the manometer registered atmospheric pressure for weeks subsequently. In most of these patients a persistent positive intraperitoneal pressure was finally attained. This phenomenon must be attributed to a prompt but limited accommodation by the muscles of the abdominal wall. In some patients a persistently positive level of pressure changed to a persistently atmospheric level when the general condition became very poor and the preterminal stage was reached. I wish to call attention to a few instances in which, after a prolonged period of positive manometer readings, an atmospheric pressure was noted on one occasion and was followed by continued positive readings on subsequent occasions. I am of the opinion that this unusual occurrence was not due

to a sudden drop in the intraperitoneal pressure but rather to faulty technic. It is probable that the end of the needle was blocked by some of the abdominal contents, most likely by the omentum or the intestinal wall.

Manometric oscillations corresponding to the two respiratory phases were commonly observed after the injection of moderate amounts of air. The usual range of oscillations was from 1 to 3 cm. after injection of 500 cc. of air, but a minimum oscillation of 4 cm. and a maximum oscillation of from 5 to 9 cm. were recorded in several cases. After

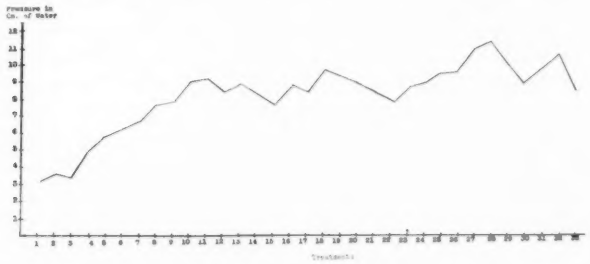

Chart 2.—Direct intraperitoneal pressure after the injection of 500 cc. of air.

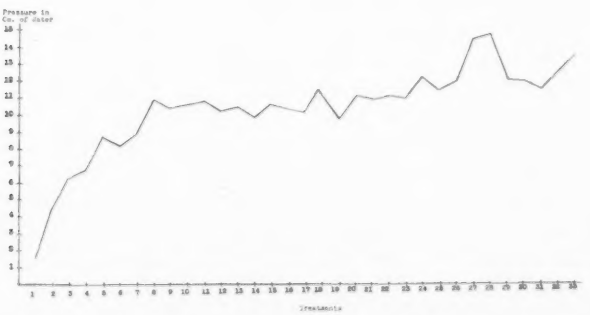

Chart 3.—Direct intraperitoneal pressure after the injection of 1,000 cc. of air.

the injection of 1,000 cc. of air the usual range of oscillations was from 1 to 4 cm., but it reached a maximum of 10 cm. in some instances. At the time of the refills, a week after previous treatments, the usual oscillation was 1 cm., but it reached a minimum of 3 cm. and a maximum of 7 cm. occasionally.

Chart 2 indicates the average intraperitoneal pressure after the injection of 500 cc. of air. It is to be noted that there is a slowly rising intraperitoneal pressure during the first few weeks; a plateau of approximately 9 cm. of positive pressure is reached in about ten weeks.

one treatment a week being given, and the pressure remains at this level, with minor changes during the subsequent course of treatment. After the injection of 1,000 cc. of air a level of 11 cm. is reached in about eight weeks, one treatment a week being given. Although marked deviations from this level were observed in some cases, it can be seen that with moderate amounts of air injected at regular intervals it was possible to obtain a constant increased intraperitoneal pressure. This increased pressure was always compatible with the patient's comfort. Empiric observations have shown [1] that this increased intraperitoneal pressure was sufficient to cause a rise of the diaphragm, which, in turn, induced therapeutically adequate relaxation of the diseased lung. I [2] have demonstrated by roentgenographic measurements that increased intraperitoneal pressure can cause reduction of the apicobasal diameter of the lung to the extent of 32.8 per cent. The clearing of extensive parenchymal lesions and the closure of large or multiple tuberculous cavities, accompanied by the disappearance of toxic symp-

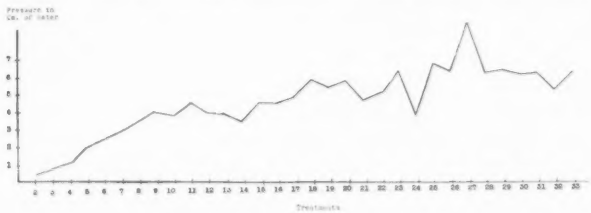

Chart 4.—Direct intraperitoneal pressure prior to periodic refills.

toms and by marked improvement in the general condition, were observed in several of the cases included in this study.

That the injection of 500 to 1,000 cc. of air at weekly intervals is capable of maintaining an elevated intraperitoneal pressure is well illustrated by chart 4. This graph shows the average intraperitoneal pressure taken at weekly intervals prior to refills. It can be seen that from the ninth week (nine injections) the intraperitoneal pressure remains at + 4 cm. or higher. This is brought about by replacement of the air absorbed from the abdomen by the blood stream and by introduction of more air into the peritoneal cavity than relaxation of the muscles of the abdominal wall is able to counterbalance.

For several of the patients, when the pneumoperitoneum was well established the treatments were continued by the subdiaphragmatic route instead of the subumbilical route used at the beginning of the

1. Banyai, A. L.: Pneumoperitoneum, Dis. of Chest **30**:8 (Dec.) 1937.

2. Banyai, A. L.: Radiological Measurements of the Apicobasal Relaxation of the Lung During Artificial Pneumoperitoneum Treatment, Am. J. M. Sc. **196**: 207 (Aug.) 1938.

treatment. The reason for this was that injection of air into the peritoneal cavity is easier by the subdiaphragmatic route. The initial manometer readings are, as a rule, lower in this region than in the hypogastrium. At the time of refill, following the injection of 500 to 1,000 cc. of air, the manometer registers either a pressure less than that below the umbilicus at the time of the preceding observation or equal to it. Transmission of the intrapleural negative pressure into the subdiaphragmatic air pocket caused substantial decrease in the manometer readings in some of the cases in this study. These observations, however, must be qualified by recognition of the fact that the varying respiratory efforts of the patient may have caused differences in pressure.

It is worthy of recording that for 1 of my patients, a 46 year old woman with far advanced pulmonary tuberculosis involving all the lobes, artificial pneumoperitoneum was discontinued after eleven weeks' treatment and was reestablished eight months later. Manometric readings showed no indication that adhesions had caused diminution in the size of the potential peritoneal space. It was also interesting to note that of the 20 patients in whom unilateral surgical paralysis of the phrenic nerve had been produced prior to pneumoperitoneum treatment, the manometer readings were unusually low before periodic refills for 14 and after periodic injections of 1,000 cc. of air for 8 patients.

CONCLUSIONS

Observations are presented to illustrate the changes in the intraperitoneal pressure during the clinical application of artificial pneumoperitoneum. It is demonstrated that in spite of the accommodation by the muscles of the abdominal wall, including the diaphragm, injections of moderate amounts of air (500 to 1,000 cc.) administered at regular intervals are capable of inducing elevation of the intraperitoneal pressure. This sustained increase of intraperitoneal pressure is compatible with the patient's comfort and is conducive to therapeutically useful relaxation of the tuberculous lung.

A VARIABLE SYMPTOM COMPLEX OF UNDETERMINED ETIOLOGY WITH FATAL TERMINATION

INCLUDING CONDITIONS DESCRIBED AS VISCERAL ERYTHEMA GROUP (OSLER), DISSEMINATED LUPUS ERYTHEMATOSUS, ATYPICAL VERRUCOUS ENDOCARDITIS (LIBMAN-SACKS), FEVER OF UNKNOWN ORIGIN (CHRISTIAN) AND DIFFUSE PERIPHERAL VASCULAR DISEASE (BAEHR AND OTHERS)

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The medical literature contains descriptions of a condition characterized by all or many of the following features: prolonged fever, polyarthritis, polyserositis, endocarditis, erythematous cutaneous lesions, nephritis, anemia and a remittent cachectic course, with a fatal termination months to several years after the onset. This variation in the characteristics and the unknown cause of the condition have resulted in the application of a great variety of names to this syndrome, depending on the symptom complex or pathologic lesion which most impressed each author. The purpose of this communication is to present a similar case with necropsy studies.

REVIEW OF THE LITERATURE

The association of visceral lesions with diseases of the skin has long been recognized. The reports by Osler [1] in 1904 of 2 cases of "visceral manifestations of the erythema group of skin diseases" may be early descriptions of the condition under discussion. When case reports [2]

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1. Osler, W.: The Erythema Group of Skin Diseases [cases 19 and 26], Am. J. M. Sc. **127**:1 (Jan.) 1904.

2. (*a*) Mook, W. H.; Weiss, R. S., and Bromberg, L. K.: Lupus Erythematosus Disseminatus, Arch. Dermat. & Syph. **24**:786 (Nov.) 1931. (*b*) Weidman, F. D., and Gilman, R. L.: A Case of Acute Disseminated Lupus Erythematosus, Necropsy Disclosing Acute Endocarditis, But Not Tuberculosis, Brit. J. Dermat. **43**:641 (Dec.) 1931. (*c*) Rose, E., and Goldberg, L. C.: Visceral Lesions of Acute Disseminated Lupus Erythematosus, M. Clin. North America **19**:333 (July) 1935. (*d*) Keefer, C. S., and Felty, A. R.: Acute Disseminated Lupus Erythematosus: Report of Three Fatal Cases, Bull. Johns Hopkins Hosp. **35**:294 (Sept.) 1924.

of "lupus erythematosus with systemic or visceral lesions" are reviewed, syndromes are occasionally encountered which strongly resemble those in the 2 cases reported by Osler. Similar conditions have been found associated with erythemas other than lupus erythematosus [3] and with purpura.[4]

In 1911 Libman [5] first recognized the existence of a peculiar clinicopathologic entity, which he and Sacks [6] reported on in 1924 as "a hitherto undescribed form of valvular and mural endocarditis" or "atypical verrucous endocarditis." Prolonged fever, serositis, arthritis, endocarditis, nephritis and, in 2 of the 4 cases, facial lupus erythematosus were the outstanding features. In 1932 Gross [7] presented the pathologic data on the heart in these cases, adding reports of 7 other cases. The relation of the so-called Libman-Sacks syndrome to dermatologic manifestations and to lupus erythematosus particularly has recently been discussed.[8]

Two instances of this symptom complex were reported by Tremaine [9] in 1934 as "subacute Pick's disease (polyserositis) with polyarthritis and glomerulonephritis" and by Christian [10] as examples of "long-continued fever with inflammatory changes in the serous and synovial membranes and eventual glomerulonephritis, a clinical syndrome of unknown etiology."

Recently Baehr, Klemperer and Schifrin [11] recorded 23 cases of disseminated lupus erythematosus associated with diffuse peripheral

3. McEwen, E. L.: Erythema Multiforme: Report of a Case with Necropsy Findings and Deductions, Arch. Dermat. & Syph. **13**:331 (March) 1926.

4. Friedberg, C. K., and Gross, L.: Nonbacterial Thrombotic Endocarditis Associated with Acute Thrombocytopenic Purpura, Arch. Int. Med. **58**:641 (Oct.) 1936. Baehr, G.; Klemperer, P., and Schifrin, A.: An Acute Febrile Anemia and Thrombocytopenic Purpura with Diffuse Platelet Thrombosis of Capillaries and Arterioles, Tr. A. Am. Physicians **51**:43 (May) 1936.

5. Libman, E., cited by Gross.[7]

6. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch. Int. Med. **33**:701 (June) 1924.

7. Gross, L.: The Heart in Atypical Verrucous Endocarditis (Libman-Sacks), in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman, New York, International Press, 1932, vol. 2, p. 527.

8. Belote, G. H., and Ratner, H. S. V.: The So-Called Libman-Sacks Syndrome: Its Relation to Dermatology, Arch. Dermat. & Syph. **33**:642 (April) 1936.

9. Tremaine, M. J.: Subacute Pick's Disease (Polyserositis) with Polyarthritis and Glomerulonephritis: A Report of Two Fatal Cases, New England J. Med. **211**:754 (Oct. 25) 1934.

10. Christian, H. A.: Long-Continued Fever with Inflammatory Changes in Serous and Synovial Membranes and Eventual Glomerulonephritis: A Clinical Syndrome of Unknown Etiology, M. Clin. North America **18**:1023 (Jan.) 1935.

11. Baehr, G.; Klemperer, P., and Schifrin, A.: A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus and Endocarditis), Tr. A. Am. Physicians **50**:139 (May) 1935.

vascular lesions and frequently polyserositis and endocarditis as instances of a "diffuse disease of the peripheral circulation." Friedberg, Gross and Wallach,[12] in 1936, discussed 4 cases of "non-bacterial thrombotic endocarditis associated with prolonged fever, arthritis, inflammation of the serous membranes and widespread vascular lesions."

ANALYSIS OF CASES REPORTED WITH POSTMORTEM DATA

It is evident that a complete review of all the cases reported of this symptom complex is impossible because of the lack of definitely established diagnostic criteria by which to determine which cases should be included. However, with most of the outstanding clinical and pathologic features accepted as criteria, selection was made of 17 cases with postmortem data. Unfortunately the 23 cases described by Baehr and his associates [11] were not reported individually, necessitating their exclusion. Other observations,[13] sometimes without pathologic studies, showed occasional similarities, but these were not sufficient to warrant inclusion of the cases in this analysis. It is possible that certain features have been overemphasized or that extraneous syndromes have been included.

1. *Incidence.*—This symptom complex is certainly not common, but it seems a fair assumption that most large hospitals at one time or another have had several patients with this type of disorder.[7] Cannon [14] has seen 3 patients with this symptom complex in private practice in two years and has stated that there have been 8 such patients at the New York Presbyterian Hospital during the past few years. The condition appears to have a marked predilection for females, as few typical syndromes occurring in males have been reported.[6] Sixteen of the 17 cases selected for analysis were of females between the ages of 8 and 48 years. The ages in 13 of the cases ranged between 19 and 37 years, and the average age was 26.2 years.

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12. Friedberg, C. K.; Gross, L., and Wallach, K.: Non-Bacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes, and Widespread Vascular Lesions, Arch. Int. Med. **58**:662 (Oct.) 1936.

13. Stokes, J. H.: The Diagnosis of Disseminated Erythematous Lupus [case 3]. M. Clin. North America **10**:290 (Sept.) 1926. Thursfield, H.: The Skin Affections Occurring in Bright's Disease, Med.-Chir. Tr., London **83**:221 (Aug.) 1900. Lancaster, L.: On Eight Cases of Uraemic Eruption of the Skin, Tr. Clin. Soc. London **25**:49 (Aug.) 1892. Keith, N. M., and Rowntree, L. G.: A Study of the Renal Complications of Disseminated Lupus Erythematosus: Report of Four Cases, Tr. A. Am. Physicians **37**:487 (May) 1922. Osler.[1] Rose and Goldberg,[2c] cases 1 and 2. Keefer and Felty,[2d] cases 2 and 3. Mook, Weiss and Bromberg,[2a] case 2.

14. Cannon, A. B., in discussion on Belote and Ratner.[8]

2. *Duration.*—The duration of the symptom complex ranged from four and one-half to forty-eight months, averaging about eighteen months. Correlation of duration with severity and extent of pathologic lesions could not be demonstrated; some of the most severe lesions occurred in cases in which the clinical course could not be traced back farther than six months. There was a suggestion that nephritis was slightly less common in those cases in which the course was of shorter duration.

3. *Clinical Features.*—The course of clinical events was sufficiently inconstant and atypical of other diseases so that the diagnosis was established only after a period of months, during which time other conditions were excluded. The onset was gradual and most often was characterized by arthralgia and fever. Less common chief complaints were of facial eruption, precordial pain, dyspnea, palpitation, malaise, weakness, loss of weight, chills, sweats, cough, sore throat and abdominal pain. After this, various signs of widespread disease gradually appeared; there was progressive weakness, despite remissions, with death occurring as a result of uremia, pneumonia, cerebral or cardiac accidents or less well defined conditions.

Articular manifestations were present at one time or another in all 17 cases. Sometimes migratory polyarthritis continued for months, with pain, stiffness, swelling and less commonly increased temperature of the affected part. Local change in color was rarely noted.[15] In a few instances there were late deformities, usually of the smaller joints of the extremities.[16] These manifestations did not seem to respond to the usual therapeutic measures.

Inflammation of the serous membranes of the pleural, pericardial and peritoneal cavities was of common occurrence. All 17 patients showed some evidence of pleuritis. The involvement of the serous membranes manifested itself by pain, friction rubs and signs of effusion. These occurred early or late in the illness. Of the friction rubs, the most frequently recorded were pericardial. Sometimes serositis was not discovered during life. In a few instances persistent abdominal pain remained unexplained after postmortem examination.[12] In 1 case the chronic peritoneal inflammation was sufficiently extensive to cause marked lymphatic and venous obstruction.[2a] It was common for signs of pulmonary involvement to be present for many months. Bronchopneumonia occurred occasionally during the course of the illness but was most frequent as a terminal condition.

15. Libman and Sacks.[6] Friedberg, Gross and Wallach.[12]
16. Tremaine.[9] Friedberg, Gross and Wallach.[12]

All the patients except the 2 with symptoms of shortest duration [17] showed evidence of increasing anemia. Endocarditis occurred in 12 of the 17 patients. The clinical signs varied widely. In 1 case the only clues were persistent tachycardia and fever.[6] The most frequent findings were blowing apical systolic, rough precordial systolic or soft pulmonary diastolic murmurs, occasionally with thrills. Except for gallop rhythm and extrasystoles, arrhythmia was absent. Electrocardiographic changes were not constant; left axis deviation, tachycardia and low voltage were the most frequently reported.

Thirteen of the patients had erythematous lesions, and when these were severe they seemed to become manifest early in the course. Facial lesions, involving the nose and adjacent areas of the cheeks to produce a butterfly-shaped pattern, were the most common. This type of lesion was usually diagnosed as acute diffuse lupus erythematosus, but on several occasions the question was raised whether it might be some other form of erythema, such as erythema multiforme.[8] The erythema involved the hands, less frequently the rest of the extremities, occasionally the chest or back and rarely the palate and buccal membranes. The cutaneous eruptions were usually described as being diffusely red and painless. Sometimes they were bluish red, raised, indurated, bullous or atrophic, with extensive scarring and pruritus. If their occurrence was remittent, a dusky brownish discoloration of the skin sometimes developed at the site of the original lesion. Alopecia was mentioned in 3 cases.[2a, c] On several occasions initiation or exacerbation of the dermatitis followed exposure to sunlight or ultraviolet rays.[2c] There was mention of repeated severe sunburn or other forms of dermatitis in the past history of some of the patients.[18]

Crops of white-centered or red petechiae were present in 6 of the 12 cases in which there was endocarditis, the former variety occurring in 3 instances.[15] The most common location was on the conjunctiva, although rarely the petechiae were generalized.[6] Once, transient tender erythematous nodes on the digits (Osler nodes) were described.[6] In another instance small subcutaneous nodules, with no microscopic evidence of associated rheumatic fever, were present on the backs of the hands.[12] Purpuric spots, noted in 4 cases, usually appeared on the trunk or the extremities.[17]

Nine of the patients had nephritis, and nearly all the rest had symptoms and signs of disturbed renal function. Two of the patients died in uremia.[19] Two had the nephrotic syndrome.[20] The blood pres-

17. Rose and Goldberg.[2c] Libman and Sacks.[6]
18. Mook, Weiss and Bromberg.[2a] Tremaine.[9]
19. Libman and Sacks.[6] Tremaine.[9]
20. Belote and Ratner.[8] Tremaine.[9]

sure was moderately elevated in an occasional case. The spleen was reported enlarged at postmortem examination in 8 cases but was palpable ante mortem in only 3 of these.[2c, d] Signs of splenic infarction were noted once,[6] although pathologically infarction was demonstrated in 5 cases. In about a fourth of the 17 cases mention was made that the edge of the liver was palpable, from the costal margin to 8 cm. below. Icterus was absent. There seemed to be no relation between hepatic enlargement and ascites.

In more than half the cases general adenopathy was noted. The lymph glands were slightly tender; they were not adherent to the skin, subcutaneous tissues or one another and were rarely greatly enlarged. The mucous membranes presented various abnormalities. In almost half the cases there was sore throat, with injection but no remarkable exudation. In several instances minute, pinpoint erosions or vesicles were present.[20] About a fourth of the patients showed pyorrhea or gingivitis. Rigidity of the neck with Kernig's sign was present in 2 cases, associated with a normal spinal fluid.[6] No abnormal mental state was noted. There was no clinical evidence of pancreatic, thyroid or other metabolic disease.

4. *Laboratory Data.*—No mention was made of anemia in the 2 cases of shortest duration (five months or less);[17] except for these there was always progressive anemia, sometimes less than 2,000,000 erythrocytes per cubic millimeter being recorded, with a correspondingly low hemoglobin level and with blood smears typical of secondary anemia. Leukocyte counts varied from 1,400 to 30,000 cells per cubic millimeter. In only 3 cases was the leukocyt count fairly consistently below 5,000, being 1,400, 2,800 and 3,200, respectively.[2a, e] Several times mention was made that the leukocyte count did not rise above normal limits, despite a high temperature and signs of sepsis. Differential leukocyte counts and the appearances of the cells were not significantly changed. Estimations of the platelet count, bleeding and clotting times and clot retraction and the results of the tourniquet test were also within normal limits.

Repeated culture of the blood was made in every case, a wide variety of aerobic and anaerobic mediums being used. In 1 instance ten cultures were made over a period of eight months.[8] In all 17 cases culture of the blood was repeatedly sterile.

Various chemical analyses of the blood showed no significant changes except for an increased urea nitrogen content in the cases in which there was azotemia.[19] In 3 cases, in each of which there was impaired renal function, hypoproteinemia (4 Gm. per hundred cubic centimeters), with reversal of the albumin-globulin ratio, was recorded.[16] Serologic studies were of no consequence. One patient showed an alternately

positive and negative reaction to the gonococcus complement fixation test;[9] another showed a repeatedly positive reaction to the Wassermann test, which did not change after intensive antisyphilitic treatment and which was not associated with a history or clinical evidence of syphilis.[12] Agglutination tests for Bacillus typhosus and paratyphosus A and B and Bacillus melitensis gave negative results.

Albuminuria, red or white blood cells and various types of casts were practically constant urinary findings. Patients with marked impairment of renal function exhibited progressive oliguria and fixation of the specific gravity, ranging from 1.013 to 1.018. In the only instance in which studies were made of the protein content of serous fluid, there were no significant findings.[9] Examination of the sputum, stool and spinal fluid and intracutaneous tuberculin tests were not of significance. One determination of the basal metabolic rate in 1 case gave a value of + 7 per cent.[28]

5. *Pathologic Data.*—There were no pathologic features which were consistently present in every case except pleuritis.

(*a*) Serous Membranes: The serous membranes seemed to be especially involved in this syndrome. Pleuritis, with or without effusion, was a constant feature. In addition, there were few cases in which changes in the pericardial or peritoneal membrane were not present. All stages of acute or chronic inflammation could be demonstrated. Fluid was most often present in one or both pleural cavities, in amounts of less than 500 cc. Ascites was somewhat less frequent, and pericardial effusions were rarely observed.[6] Apparently cardiac failure, renal impairment or hypoproteinemia played a minor role in the production of such effusions. Marked evidence of chronic inflammation was frequently observed. Thus there was sometimes obliteration of the pleural or pericardial spaces with fibrous tissue, occasionally accompanied by perisplenitis or perihepatitis. Several times the descriptions indicated that these adhesions were edematous and easily torn apart, showing a loose connective tissue, with plasma cells, lymphocytes and eosinophils infiltrating the area.[16] Chronic inflammation was occasionally limited to a small area, such as the upper portion of the abdomen, the mesenteric folds or the costophrenic angles.

Despite the frequent clinical indications of synovial involvement, pathologic studies of joints were rarely reported. In 1 case hypertrophy of synovial villi, subperiosteal bone formation and inflammation with perivascular infiltration of the surrounding tissue were reported;[9] while in another instance similar articular and extra-articular swelling was observed along with endothelial proliferation and a small amount of dirty yellow fluid containing giant cells and a few gram-positive

cocci.[12] In the latter case there were spindle-shaped phalangeal deformities. In another case there was moderate edema of the capsule of the right knee joint.[12]

(*b*) Heart: There were no constant pathologic changes in the heart. The organ was usually enlarged, with varying degrees of muscle changes: edema, lymphocytic infiltration, small hemorrhages, parenchymatous degeneration, acute degenerative myocarditis or sometimes replacement fibrosis. In some cases the endocardium was smooth and without evident lesion. At times the atypical verrucous endocarditis of Libman and Sacks[6] was mentioned. These vegetations, usually larger than rheumatic changes, were grayish, pinkish or yellowish and verrucous, with a tendency to spread to the mural endocardium, papillary muscles, chordae tendineae and sometimes the auricle, usually the left. These were unassociated with such evidences of rheumatic infection as Aschoff bodies. In 2 of these cases all four valves were involved.[6] In other cases there were smaller vegetations, the size of a pinhead, composed of thrombi with platelets, slightly covered with endothelium and without spread of the growth to the auricular or ventricular endocardium. Exudative fibrinous deposits, fibrous thickenings and granular and hyaline changes in the valves have also been reported. In none of the cases of endocarditis was there a marked inflammatory reaction of the valve; usually there were only small scattered areas of organization at the bases of the vegetations. In several cases chronic valvular changes, questionably rheumatic, were noted.[12] Culture of vegetations or heart blood was sterile except for the isolation of Streptococcus haemolyticus, Staphylococcus aureus and Bacillus alcaligenes faecalis from three large vegetations present in the case reported by Weidman and Gilman.[2b] All 12 patients with endocarditis showed some change in the mitral valve, and the tricuspid and aortic valves were each involved in half the cases, frequently together.

(*c*) Blood Vessels: Minute vascular lesions in the systemic and sometimes in the pulmonic circulation were stressed in this syndrome by Baehr and his associates,[11] who postulated that a progressive process might have occurred from simple capillary dilatation and thrombus formation with endothelial proliferation to degenerating, necrotizing lesions in the walls. Sometimes these changes were widespread. In 9 of the 17 selected cases under discussion the vascular changes were prominent enough to be mentioned. In 1 case the vascular lesions were considered typical of periarteritis nodosa.[12] In others there was thickening of the walls of only a few arteries, as in the spleen or kidney, or there were hyaline or granular plugs with fibrosis and recanalization. Sometimes all the coats of the vessel exhibited focal or diffuse necrosis.

destroying all semblance of a normal artery. Rarely, the veins showed medial degeneration with surrounding infiltration.[12] The cellular response to such changes was not unusual.

(*d*) Kidneys: In 9 of the 17 cases under discussion there seemed to be true glomerulonephritis, and in 7 there were renal vascular changes of sufficient severity to be mentioned in the reports. Both patients dying with azotemia [19] had vascular alterations and some renal infection, in addition to glomerulonephritis. There were 2 additional cases, not classified as cases of nephritic involvement, in which renal vascular changes were present.[15] In the remaining 6 cases there were unusual urinary findings for which only congestion, minute hemorrhages or parenchymatous degeneration could be demonstrated. Of the 2 patients exhibiting the nephrotic syndrome, 1 [9] had glomerulonephritis with fatty droplets in the tubules and hyaline deposits in the basement membranes of the tubules, and the other [8] showed chronic pyonephritis with "tubular nephrosis." Subcapsular abscesses, from which staphylococci were usually isolated, were recorded in 4 cases.[21]

A distinct type of renal alteration, apparently dependent on vascular changes, has been described in connection with this syndrome by Baehr and his associates.[11] In 20 of the 23 cases reported, there were conspicuous renal vascular changes. Glomerular proliferation and thrombosis were present in 18 cases, and in 13 of these there was almost complete hyalinization of the glomerular capillaries without lipoid or amyloid deposition, which they termed a "wire-loop" lesion. Glomerular hyalinization was not stressed in the 17 cases under discussion.

(*e*) Other Organs: Thirteen patients had pulmonary consolidation, and the remaining 4 exhibited congestion or partial collapse of the lungs. While the consolidation approached lobar extent in a few instances, in the majority of cases it was patchy and bilateral, presenting the usual picture of bronchopneumonia. The spleen was enlarged in 8 instances, in 5 cases being associated with infarction. Hemosiderosis, congestion and acute hyperplasia were usually present, and the capsule was occasionally thickened, sometimes with the edematous adhesions previously mentioned. Sepsis was present once.[2c] There were likewise no characteristic changes in the liver: the weight was not remarkable, parenchymatous degeneration and congestion were common and thickening of the capsule was recorded 6 times. In a few cases focal necroses were present.[22] In most instances the lymph glands of the thorax or abdomen were somewhat enlarged, exhibiting various stages of acute and chronic inflammation. The enlargement was rarely massive, seemingly being

21. Weidman and Gilman.[2b] Keefer and Felty.[2d] Libman and Sacks.[6] Tremaine.[9]

22. Mook, Weiss and Bromberg.[2a] Libman and Sacks.[6] Tremaine.[9]

due to edema.[2d] The only lesions noted in the few cases in which the brain was examined were edema and degeneration.[16] The rest of the autopsy data, including several reports of pathologic changes in the skin, [2a,d] were so varied that correlation was impossible.

(*f*) Tuberculous Lesions: Tuberculous foci were observed in 4 instances: in an axillary node,[2d] in mediastinal and tracheobronchial nodes,[6] in tracheobronchial nodes and the lungs [2a] and in mesenteric nodes.[9] Only the last lesion was described as "healed"; the rest were caseous. In none was there dissemination of infection, as far as could be determined.

REPORT OF A CASE [23]

M. A., a woman aged 26, was admitted to the Syracuse Universitiy Hospital on Nov. 20, 1935, complaining chiefly of soreness in the chest and cough of four weeks' duration.

History.—The patient was born in Kansas and came to New York five years before admission to the hospital. Her family history was not remarkable except that one grandmother died of valvular heart disease. Her father was living but had "rheumatism"; her mother, five sisters and four brothers were living and well. The patient resided on a farm with her parents; she had been a clerk in a clothing store in a small community for the past four years. As a child she had chickenpox, measles, pertussis, scarlet fever, pneumonia and some undetermined disease of the skin which resulted in scars on the left anterior wall of the chest. In 1918 she had a mild attack of influenza. In 1927 she was at home in bed for two months with painful swelling of the left leg, which she stated did not involve the joints. She recovered without any apparent residual condition. She denied having a venereal infection. She said she slept eight hours each night; used no drugs, alcoholic beverages or tobacco, and took an emulsion of liquid petrolatum with agar and phenolphthalein daily as a laxative. She had had no injuries, roentgen examination, operation or hospitalization, and the review of the systems showed essentially no abnormality prior to the present illness. Her weight was 140 pounds (63.6 Kg.) at the time of onset. The catamenia was not remarkable.

The present illness began in the fall of 1934, with an indefinite attack of soreness of muscles and pain in the joints, involving the knees, ankles, wrists, shoulders, elbows, back and fingers. This illness persisted as a chronic condition with occasional pains in the joints and increasing lassitude, but the patient was able to continue her work. In July 1935 she complained of occasional pains in the joints, marked malaise and lassitude which forced her to bed. She had a low grade fever, a temperature of 99 to 100 F. On Aug. 10, 1935,[24] she had a temperature of 99.4 F., a pulse rate of 112, a blood pressure of 118 systolic and 80 diastolic and a body weight of 129 pounds (58.6 Kg.). The findings were not remarkable except for enlargement of the joints of the fingers, the chest was clear and the spleen was not palpable. The hemoglobin (Dare) value was 65 per cent. The urine showed albumin (1 plus), with an occasional pus cell and hyaline cast. The

23. This patient was seen by us at the Syracuse University Hospital.

24. The patient's history and the report on the examinations and course prior to her admission to the Syracuse University Hospital were supplied by Dr. A. N. Curtiss.

Wassermann test of the blood gave a negative reaction. Culture of the blood showed no growth, and there was no serum agglutination for B. typhosus and Brucella melitensis.

Her condition remained the same until September, when she became acutely ill, with a temperature varying between 101 and 102 F. nearly every day and a pulse rate as high as 150. In November there were signs of enlargement of the heart, with cardiac failure. There was a loud friction rub in the left axilla, which changed to bronchial breathing and moist rales. For two weeks prior to entry the patient had a sore throat, enlargement of the glands of the neck and the axilla, a palpable spleen and stridorous breathing. For several days there was a cough, with small amounts of yellowish sputum, never blood streaked. The signs in the chest increased, and the liver became palpable 3 fingerbreadths below the costal margin. During this period the leukocyte count varied between 5,000 and 8,000, with a normal differential count. Serum agglutination tests for B. typhosus, B. paratyphosus, Br. melitensis and Bacillus tularensis gave a negative reaction. The reaction to the Wassemann test of the blood remained negative. Salicylates had been tried in large doses for over a month, without effect.

Admission to the Hospital.—On Nov. 20, 1935, the patient was admitted to the Syracuse University Hospital. In addition to the history which has already been given, the patient complained of some recent loss of hearing and stated that in July 1935 she had a few severe night sweats just prior to going to bed. She had had moderate dyspnea during the past year. There was no history of chills.

Physical Examination.—Physical examination on entry revealed a temperature of 102 F., a pulse rate of 112, a respiratory rate of 22 and a blood pressure of 138 systolic and 90 diastolic. The patient was well developed and fairly well nourished. She was lying quietly in bed, apparently acutely ill but in no discomfort. On the face there was an erythematous area, extending over the nose to the lower part of the cheeks. The skull showed no exostoses, the scalp was profusely covered with brown hair and there were no scars. The pupils were equal and regular and reacted to light and in accommodation. The external ocular movements were normal, the media were clear, the disks were normal, the retinas were not unusual, except for a few fine granular changes in the maculas, and the retinal vessels appeared rather thick for the patient's age. The ears and the nose were not remarkable. There was dilatation of the alae nasi with each inspiration. The teeth were carious, the tongue was coated brown, the throat was red and inflamed and the tonsils were small and fibrous. There was no rigidity of the neck. The thyroid gland was not palpable. There were enlarged, tender suboccipital and posterior cervical glands, more marked on the left; the axillary and inguinal glands bilaterally were enlarged and tender, being the size of a pea or larger. The thorax was symmetrically developed, with equal, rapid, shallow expansion. There were five scars about 1 inch (2.5 cm.) long on the skin of the upper right side of the chest. The breasts were normal, with no masses. There was flatness to percussion in the left axilla, the base of the left lung and below the angle of the right scapula; the upper part of the left side of the chest anteriorly was hyperresonant. In the flat areas there were bronchial breathing, increased whispered voice sounds and increased tactile fremitus; there were crepitant rales at the base of the left lung. The heart was enlarged to the left, with the sounds fast and forceful but of regular rate, force and rhythm; there was a soft systolic murmur at the mitral area. The abdomen was distended and tympanitic, with the liver palpable 4 fingerbreadths and the spleen 3 fingerbreadths below the costal margin. There was slight tenderness in the

epigastrium. There were no other masses or any evidence of fluid. The extremities showed moderate wasting of the muscles; there was no peripheral edema. The superficial reflexes were present and hyperactive, no pathologic reflexes were elicited, there was no clonus, and coordination and the vibratory sensation were intact. The skin was emaciated and dehydrated, with no rash apparent except on the face; there were no petechial spots. There was a small, red decubital area over the coccyx. The vulva was normal, with no discharge; the Skene and Bartholin glands were normal. The cervix was small, and it pointed in the center of the canal and showed normal mobility and no tenderness. The fundus was normal, with second degree retroversion, but was freely movable and not tender. In the adnexial regions there was no mass, thickening or tenderness.

Laboratory Examination.—At the time of entry laboratory studies revealed: hemoglobin, 78 per cent (12 Gm.); erythrocytes, 3,500,000, and leukocytes, 11,600 per cubic millimeter, with 82 per cent polymorphonuclear cells and the rest of the differential count normal. The red blood cells were poorly filled. The urine was brown, cloudy and acid, with a specific gravity of 1.022, albumin (4 plus), sugar (1 plus) and no acetone or diacetic acid. There were numerous pus cells, hyaline and granular casts and red blood cells. A serum agglutination test for B. typhosus showed a reaction in low dilution only, probably of negligible significance. Roentgen examination of the chest revealed increased markings in the right lung, with thickening of the right interlobar pleura, with no evidence of true massive consolidation. The left lung showed opacity in the base, with loss of the cardiophrenic and costophrenic angles. The cardiac shadow was increased in width, with the angles rounded. The impressions of the roentgenologist were: (1) pneumonitis with partial consolidation in the lower lobe of the left lung, (2) pneumonitis with partial consolidation in the lower portion of the upper lobe and in the middle lobe and slight invasion of the lower lobe of the right lung, (3) probable pericarditis with effusion and (4) possibly pleuritic fluid in the lower portion of the left lung.

Course.—The patient was given symptomatic treatment for the cough and the distention. She took fluids well. The next day she appeared more alert, with the dehydration diminishing and the distention entirely relieved. The spleen was readily palpable, the pharyngitis was improved and the lymph nodes were less tender. Salicylates were administered in large doses. Two days after admission to the hospital there was little change in the roentgen appearance of the chest. The patient felt much improved at the end of a week. Her temperature had continued at approximately 99 F. At this time a transfusion of citrated blood was given. At the end of two weeks she was still improving, with the temperature normal and the intake and output of fluids good.

On examination on the nineteeth day in the hospital the face was flushed; the cervical and axillary glands were large and not tender and were easily mobile under the skin; the inguinal and epitrochlear glands were not enlarged. No petechiae were seen on the conjunctiva, mouth or skin about the neck or chest; however, the skin showed numerous diffuse, red, macular spots resembling rose spots. There was dulness at the apex of the right lung anteriorly and at the base of the left lung posteriorly; there were bronchial breathing and bronchophony at the base of the left lung. The heart beat was regular, with the apex in the fifth interspace at the midclavicular line; no murmurs were heard, but the second mitral sound was rather sharp. When the patient was turned on her left side a soft mitral systolic murmur was heard; the pulmonic second sound was not accentuated. The spleen was enlarged and firm, with a rather sharp edge; the edge of the liver was just palpable; the abdomen was soft and not dis-

tended. There was a firm swelling in the region of the left sacroiliac joint, which was not red or especially tender. The similarity of the course of the patient's illness to that of Osler's disease, Libman-Sacks disease, Baehr's disease and disseminated lupus erythematosus was suggested at this time by one of us (E. C. R. Sr.).

The next day the patient was moved into another room in order to be exposed to more sunlight. Careful peripheral vascular studies were undertaken twenty-two days after her admission to the hospital. Slight cyanosis was noted when the hands were in a dependent position; normal oscillometric curves were obtained for both arms and low amplitude curves for both legs. There was palpable pulsation in all the vessels. These observations were felt to represent general inanition and low pulse volume rather than obliterative vascular disease. The following day a red area the size of a silver dollar over the right sacroiliac joint was incised, and a large amount of pus was removed. Staph. aureus was present.

Four days after exposure to sunlight there was a marked increase in the intensity of the bluish red discoloration of the cheeks, and maculopapular, deep red areas the size of a pea appeared on the left buttock. The following day there were scaly, red erythematous areas with whitish crusts on the lower lobe of the right ear. The biopsy of a small gland from the neck revealed "chronic lymphadenitis." For several weeks her temperature had varied between 99 and 100 F., with the pulse rate between 86 and 104 and the respiratory rate between 18 and 24. Four weeks after her admission to the hospital, culture of nasal secretion was positive for diphtheria, but an epidemiologist could find no clinical evidence of diphtheria. Culture of material from the throat was sterile. A brother of the patient, who was visiting her, complained of a sore throat; he was found to have a red pharynx and large congested tonsils but no diphtheritic membrane, and culture of material from his nose and throat was sterile.

Twenty-nine days after her admission to the hospital and nine days after her exposure to sunlight was increased, the thoracic condition was much improved, but she appeared drowsy and slightly disoriented and complained of pain in the legs. Her temperature had risen to 105 F., the pulse rate was 136, the respiratory rate was 24 and the blood pressure was 108 systolic and 86 diastolic. Her temperature continued to be elevated for three days, and during this period she had "nightmares and cried out in her sleep." She appeared frightened and despondent. The glandular enlargement was disappearing, but the spleen was still palpable. She was moved to a darker room. Five weeks after her entry the temperature was varying between 100 and 103 F. She appeared weaker, had no appetite, had occasional abdominal distention and complained of headache and other vague aches and pains. Her weight had fallen to 100 pounds (45.4 Kg.).

Six weeks after entry there were more cutaneous lesions, particularly on the back and the side of the neck; there were a few on the abdomen and several on the legs. The lesions were not elevated; some were covered with scales and were a dusky copper color, about 1 cm. in width and not painful. Several were herpetic, and there was evidence of herpes of the lips. The apex beat was outside the midclavicular line, no murmurs were heard, there were moist rales at the base of the left lung, and the liver and spleen were palpable. Roentgen examination of the chest showed inflammatory change in the lower field of the left lung without displacement of the heart, and there was thickening of the interlobar pleura on the right side. The patient had frequent emeses of dark fluid and was unable to retain any liquid by mouth. Her temperature was normal, the pulse rate was 80 and the respiratory rate 20. The blood pressure

had fallen from the level on entry, of 138 systolic and 90 diastolic, to 90 systolic and 60 diastolic. The pulse rate had been varying between 80 and 130, with the high rate occurring during the episodes of fever.

Two days later the patient was failing rapidly, with labored breathing, tachycardia and muscular twitching of the arms, hands and head. There was acute distention, which could not be relieved by enemas. The patient seemed disoriented part of the time. The following day the muscular twitchings became pronounced; large, dry bronchial rales were heard over the entire chest, and the heart sounds became distant and rapid, almost fetal in character. The patient was weak, disoriented and incoherent. There was marked oliguria. Death occurred forty-three days after entry and approximately twenty-seven months after the onset of the illness.

Further Laboratory Studies.—The patient showed secondary anemia on entry which persisted throughout her stay in the hospital (ten days after entry the erythrocyte count rose to 4,500,000 per cubic millimeter but two days before death it was 3,700,000). The leukocytes numbered 11,600 per cubic millimeter on her admission to the hospital. The following day the leukocyte count was 8,800, and it continued to fall, reaching 4,800 at the end of ten days. The count persisted at approximately 5,500 until the last week, when it rose slowly to 14,200 preagonally. The polymorphonuclear count varied between 60 and 83 per cent and the lymphocytic cells between 13 and 33 per cent. There was little change in the rest of the differential count. Smears showed continually a high percentage of nonfilamented polymorphonuclears, from 32 to 67 per cent, and there were many unclassified cells. Twenty-six days after her entry the hematologist reported as follows: "A number of examinations of the blood with various stains seemed to establish the fact that this patient had a few myelocytes and premyelocytes in the smears. On one occasion a myeloblast was noted. There was always a distinct 'left-shift,' with an increase in the percentage of nonfilamented polymorphonuclears. Normoblasts were present in fair number, although only 1 might be seen in the examination of several fields. The hematologic data suggested possible blood dyscrasia or irritation of the bone marrow by neoplastic invasion, infection or toxemia." During the period when the leukocyte count was low, leukocytosis could not be stimulated by intensive liver therapy. Nine per cent premyelocytes, myelocytes and metamyelocytes were present on December 27, seven days before death. The red blood cells showed moderate anisocytosis and poikilocytosis, and a rare cell showed diffuse basophilia. On December 9 the platelet count was 260,000 per cubic millimeter.

Repeated urinalyses continued to show albumin, granular casts and white and red blood cells. Repeated specimens of urine did not show Bence Jones protein. The Mosenthal test showed a range in specific gravity from 1.012 to 1.019, with 440 cc. of urine per day and 400 cc. per night. The urine showed no abnormality on culture. The phenolsulfonphthalein test showed 75 per cent excreted in two hours. The nonprotein nitrogen content of the blood varied between 33 and 40 mg. per hundred cubic centimeters. Repeated culture of the stools revealed no organisms of the typhoid, paratyphoid or dysentery groups.

Repeated serum agglutination tests for typhoid, paratyphoid A and B, dysentery and undulant fever gave negative responses. Three cultures of blood were sterile. Blood was injected into a guinea pig, which died after two weeks; autopsy showed no lesion of any known organism. The tuberculin test gave a negative reaction at seventy-two hours. A cutaneous test for Brucella abortus gave a negative reaction at seventy-two hours. The blood serum showed no leptospiras or borrelias of the relapsing fever group by direct dark field exami-

nation or by animal inoculation. The Bunnell test for heterophile agglutinins gave a negative reaction. The gonococcus complement fixation test gave an anticomplementary reaction. The Wassermann tests of the blood of the patient, her father and her two brothers gave negative reactions.

Culture of material from the nose was repeatedly positive for diphtheria but showed no increase in hemolytic streptococci. On several occasions culture of material from the throat showed an increase in hemolytic streptococci. On December 17 culture of nasal secretion was reported as showing diphtheria; culture of material from the throat did not. The Schick test gave a positive reaction after seventy-two hours, with the control reaction entirely negative. A virulence test for diphtheria gave a negative reaction, and the final culture of material from the nose and throat gave negative results. The sputum showed no spirochetes, yeast cells or tubercle bacilli. Urethral and cervical smears did not contain gonococci. Three weeks after entry cutaneous sensitivity tests with ninety-three common protein antigens all gave negative reactions. The Friedman modification of the Aschheim-Zondek test gave a negative reaction.

The sedimentation rate (Cutler) when corrected for the anemia was still rapid, and this alteration persisted throughout the patient's stay. It increased as the illness progressed and at the end of four weeks was 21 mm. in fifteen minutes and 31 mm. in one hour. The blood sugar level during fasting varied between 62 and 81 mg. per hundred cubic centimeters. The dextrose tolerance test revealed the following values for sugar in the blood and in the urine: during fasting, 80 mg. and 1 plus respectively; at one hour, 160 mg. and 1 plus; at two hours, 117 mg. and 1 plus, and at three hours, 100 mg. and 1 plus. The serum showed the following values for protein, albumin and globulin, respectively: 8.4, 3.4 and 5.0 Gm. on December 10; 7.2, 2.8 and 4.4 Gm. on December 14; 12.1, 5.2 and 6.9 Gm. on December 18, and 8.8, 3.2 and 5.6 Gm. on December 20. The cholesterol value of the blood was 151 mg. per hundred cubic centimeters on December 11 and 103 mg. on December 20. The calcium value was 8.0 mg. on December 16 and 7.7 mg. on December 20.

The basal metabolic rate according to the Du Bois method was +41 per cent on December 11, +41 per cent on December 14 and +35 per cent on December 17. On all these days the temperature ranged between 98.8 and 100.6 F. and the pulse rate between 80 and 90. Roentgen examination of the long bones showed no pathologic condition except bilateral exostoses in the distal portion of the shaft of each fibula. The skull revealed no evidence of a pathologic condition in the vault, the frontal bones were not fused and the suture line was seen.

The electrocardiogram made on December 4 showed sinus rhythm, a rate of 110 per minute, no axis deviation, a PR interval of 0.14 second, a QRS of 0.06 second and an RT of 0.24 second. The chest lead (apex beat and left leg) was abnormal. There was low voltage in all leads, and the T wave was upright. On December 9 the findings were the same except that the RT interval was 0.22 second, the RT intervals of lead I and lead II were concordant and the rate was 100 per minute. These findings were interpreted as indicating sinus tachycardia and, because of the low voltage, probably some myocardial damage.

Examination of the spinal fluid on December 13 revealed clear, colorless fluid; 5 cells per cubic millimeter, all lymphocytes; a normal globulin value; 745 mg. of chlorides per hundred cubic centimeters, and 42 mg. of sugar per hundred cubic centimeters. The Wassermann test gave a negative reaction with both the cholesterolized and the noncholesterolized antigen. The colloidal gold curve was 1122332100 (mixture of curves of types 2 and 3), and the gum mastic test gave a positive reaction. One week later the Wassermann test of the spinal

fluid was anticomplementary. On December 22 the spinal fluid showed an increased globulin value (200 cells per cubic millimeter, chiefly lymphocytes with a few polymorphonuclears). The Wassermann test gave a negative reaction with both antigens, and the colloidal gold curve was 011125432 (type 3). Two days before death the colloidal gold curve was 0111123321 (type 3), and the gum mastic test gave a positive reaction.

Postmortem Examination.[25]—Postmortem examination revealed externally a few small, irregular, reddened, scaly, slightly elevated areas over the face, ears, back and anterior thoracic wall; a small amount of purulent drainage from the left eyelid; marked sordes in the mouth; three old, white, oblique scars over the right upper portion of the chest; a recent reddish scar along the posterior border of the left sternomastoid muscle; a deep ulcer with a reddish base on the left buttock; marked abdominal distention; slight edema of the ankles, and enlargement of the anterior and posterior cervical lymph nodes bilaterally, with no enlargement of the remaining external lymph nodes.

The peritoneal cavity contained approximately 400 cc. of clear, yellow fluid. Fibrinous adhesions were present between the diaphragm, the liver and the spleen, those about the spleen being particularly dense. There was also marked adherence between the stomach, the transverse colon and the liver. The omentum was studded with numerous small, soft whitish areas the size of a pinhead. There were many fibrinous adhesions throughout all the coils of the small intestine, and there was marked edema of the large bowel about the splenic flexure. The lymph nodes in all portions of the mesentery were markedly enlarged and showed on section reddish areas of hemorrhage.

The spleen weighed 300 Gm. The capsule was markedly thickened and edematous. When the organ was sectioned the capsule fell off the splenic substance, which was softer and slightly more grayish than usual. The malpighian corpuscles stood out rather prominently. The liver weighed 1,910 Gm. The capsule was somewhat thickened and roughened. On section the parenchyma was pale yellow, with irregular red mottling. The pancreas was somewhat enlarged, firmer than usual, of irregular shape and densely adherent to the surrounding tissue. On section the main duct of the pancreas was filled with a cheesy-like material, apparently dammed up secretion. The kidneys weighed 310 Gm. The renal substance pouted slightly beneath the capsule, and the cortex was somewhat paler than usual and presented a "cooked" appearance. The capsules stripped easily. The aorta was smooth and showed a minimal amount of yellowish thickening.

The remainder of the gastrointestinal tract, the appendix, the gallbladder and bile ducts, the adrenal glands, the organs of the pelvis and psoas muscle showed nothing unusual.

The right pleural cavity was almost completely obliterated by old and fresh fibrous and fibrinous adhesions. In the left pleural cavity, encapsulated in a pocket, was approximately 400 cc. of clear, yellow fluid. The remaining surface of the left lung also showed numerous adhesions. The left lung weighed 380 Gm. and the right 420 Gm. The lower lobe of the left lung was partially collapsed, deep reddish blue and doughy. The remaining portions of both lungs showed pulmonary edema, with numerous patchy areas which exuded fluid on pressure. The bronchi were reddened over their entire surface. The mediastinum,

25. Postmortem examination was performed at the Syracuse University Hospital on Jan. 2, 1936, by Dr. Robert O. Gregg.

the mediastinal lymph nodes, the bronchial lymph nodes, the pulmonary artery (opened in situ) and the pulmonary vessels in the lungs showed nothing unusual.

The pericardial cavity contained approximately 25 cc. of clear, amber fluid. There was one area of dense, firm adherence between the visceral and the parietal pericardium on the anterior surface of the heart, covering an area measuring approximately 5 by 5 cm. The pericardial fat was markedly edematous. The heart weighed 370 Gm. On section the myocardium was deep reddish brown and firm. The auricular appendages, the tricuspid, pulmonary, mitral and aortic valves, and the coronary arteries showed nothing unusual.

The brain weighed 1,160 Gm. The dura was less adherent to the calvarium than usual, and the pia-arachnoid was somewhat thickened, particularly about the angle between the cerebellum and the pons. There was an increased amount of cerebrospinal fluid, which was slightly turbid. On section the substance of the brain was softer, and the vessels throughout were more prominent than usual. The base of the skull, the middle ears, the pituitary gland and the thyroid gland showed nothing unusual.

Section of the sternum and ribs showed a reddish gray, hyperplastic marrow, and there were a few reddened areas in the sternal marrow, apparently due to hemorrhage. Section of the femur revealed a markedly thickened cortex and a marrow cavity not much larger in diameter than an ordinary pencil. Spicules of bone were seen extending through the marrow cavity, and this marrow appeared hyperplastic. The synovial membrane of the knee joint was smooth and light gray.

A swab from the gallbladder did not show pus or organisms, and culture yielded no growth in forty-eight hours. Culture of blood from the right ventricle (one flask, undoubtedly contaminated) yielded Staphylococcus albus and diphtheroid bacilli.

Microscopic examination[26] of the sections made post mortem revealed the following data: rib—hyperplasia of the marrow cells; marrow from the femur—moderate hyperplasia of the entire cellular structure; pancreas—a diffuse infiltration by polymorphonuclear leukocytes and necrosis of the superficial fat, without evident hemorrhage; thyroid gland—alveoli dilated and lined by low flattened cuboidal epithelium, with focal areas of hyaline degeneration scattered throughout; adrenal gland—no evident lesion other than the infiltration of a few lymphocytes and monocytes on the peritoneal surface; pituitary gland—without evident lesion; ovary—graafian follicles conspicuously absent; lymph node—a moderate degree of edema and inflammatory reaction; brain—without evident lesion; choroid plexus—without evident lesion; spleen—no noteworthy lesion; liver—considerable fatty infiltration throughout the parenchyma, with no evidence of pigment retention; kidney—moderate chronic glomerulonephritis, with recent embolic manifestations; lung—an old organized caseating tubercle with the surrounding alveoli free from the inflammatory process; bronchus—a few foci of round cell infiltration just beneath the mucous membrane; mesentery—an occasional lymph follicle showing edema and an inflammatory reaction and considerable fat necrosis but no evidence of tuberculosis; skin—slight cornification of the surface epithelium, a moderate degree of atrophy of the corium, only a rare hair follicle and an occasional sweat gland; voluntary muscle—without evident lesion.

Anatomic Diagnosis.—The anatomic diagnosis was: (1) chronic and subacute polyserositis with pleuritis, pericarditis and peritonitis; (2) acute nephritis; (3)

26. Dr. A. S. Giordano, of South Bend, Ind., made this examination.

acute pancreatitis; (4) slight adhesive meningitis; (5) splenomegaly with perisplenitis; (6) hepatomegaly with perihepatitis; (7) fatty infiltration of the liver; (8) pleural effusion; (9) bilateral pulmonary edema; (10) old organized caseating pulmonary tubercle; (11) ascites; (12) diffuse dermatitis; (13) generalized lymphadenitis; (14) hemorrhage and hyperplasia of the bone marrow; (15) thickening of the cortex of the femur and growth of bone in the medullary cavity, and (16) focal hyaline degeneration of the thyroid gland.

The microscopic sections were also compared with those made for the 2 patients reported on by Tremaine [9] and by Wolbach,[27] who stated that the liver showed peculiar delicate cellular adhesions corresponding closely to those seen in the patients reported on by Tremaine.

SUMMARY OF CASE REPORT

A 26 year old woman had a progressive cachectic illness of twenty-seven months' duration, characterized by the gradual onset of polyarthritis, malaise and remittent low grade fever, followed by pleuritis with effusion; pericarditis with effusion; myocardial failure; pharyngitis; generalized lymphadenopathy; hepatomegaly and splenomegaly; erythematous eruption of the face, left buttock, right sacroiliac region and right ear; nephritis; meningitis; ascites, and peritonitis.

Laboratory studies revealed progressive secondary anemia; hyperplasia of the bone marrow; moderate leukopenia; albumin, pus, red blood cells, hyaline and granular casts in the urine; an increased erythrocyte sedimentation rate; low levels for calcium and cholesterol in the blood; a slightly elevated serum protein content, with a reversed albumin-globulin ratio; electrocardiographic evidence of sinus tachycardia and low voltage; an elevated basal metabolic rate ($+35$ to $+41$ per cent), and abnormal findings for the spinal fluid, with an increased number of cells, an increased globulin content, a low sugar level, a type 3 colloidal gold curve and a positive gum mastic curve. Additional bacteriologic, chemical and serologic studies of the blood; bacteriologic and chemical studies of the urine, feces, sputum, spinal fluid and nasal and pharyngeal secretions, and roentgen examinations of the long bones and the skull were not remarkable.

Pathologic examination showed diffuse lesions of the skin; generalized lymphadenitis; chronic and subacute polyserositis with pleuritis, pericarditis and peritonitis; ascites; pleural effusion; hepatomegaly and splenomegaly; fatty infiltration of the liver; focal hyaline degeneration of the thyroid gland; acute nephritis; acute pancreatitis; bilateral pulmonary edema; an old organized caseating pulmonary tubercle; hemorrhage and hyperplasia of the bone marrow; adhesive meningitis, and thickening of the cortex of the femur, with growth of bone in the medullary cavity.

27. Wolbach, S. B.: Personal communication to the authors.

A Variable Symptom Complex of Undetermined Etiology with Fatal Termination; Essential Clinical Laboratory and Pathologic Features in Eighteen Cases *

Authors	Case Number	Sex	Age, Years	Duration of Illness, Mo.	Joint Manifestations (Arthritis or Arthralgia)	Pleuritis	Abnormal Urinary Findings	Anemia	Pleural Effusion	Pneumonia	Pericarditis	Peritonitis	Endocarditis	Lymphadenopathy	Lupus Erythematosus	Nephritis	Pharyngitis	Arteritis	Splenomegaly	Perisplenitis	Petechiae	Perihepatitis	Hepatomegaly	Splenic Infarct	Purpura	Tuberculosis	Alopecia	Erythemas Other Than Lupus Erythematosus	Leukopenia	Joint Deformity	Azotemia	Stiff Neck (Kernig Sign)	Nephrotic Syndrome	Meningitis	Pancreatitis	Elevated Basal Metabolic Rate
Libman and Sacks [6]	4	F	10	4½	X	X	X	?	X	X	X	X	X	X	X	—	—	X	X	X	X	—	X	X	—	X	—	—	—	—	—	—	—	—	—
Rose and Goldberg [2c]	4	F	25	5	X	X	X	—	X	X	—	—	—	X	X	—	X	—	X	—	—	—	—	—	—	—	X	—	X	—	—	—	—	—	—
Mook, Weiss and Bromberg [2a]	3	F	48	5½	X	X	X	X	X	X	—	X	—	—	X	—	—	—	—	—	—	—	X	—	—	—	X	—	—	—	—	—	—	—	—
Libman and Sacks [6]	1	F	24	6	X	X	X	X	X	—	X	X	X	—	—	X	X	—	—	—	X	—	—	X	X	—	—	X	—	—	X	X	—	—	—
	2	F	37	9	X	X	X	X	X	X	X	X	X	—	X	—	X	X	X	X	X	—	X	—	X	—	—	—	—	—	—	X	—	—	—
	3	M	19	9	X	X	X	X	X	—	X	—	X	—	—	X	—	—	X	—	X	—	X	X	X	—	—	X	—	—	—	—	—	—	—
Weidman and Gilman [2b]	..	F	19	9	X	X	X	X	X	X	—	—	X	X	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Friedberg, Gross and Wallach [13]	3	F	19	9	X	X	X	X	X	X	X	X	X	—	—	X	X	X	—	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—
	4	F	21	11	X	X	X	X	X	—	X	X	X	—	—	X	—	X	—	X	X	X	—	X	—	—	—	X	—	—	—	—	—	—	—
Tremaine [9]	2	F	32	12	X	X	X	X	X	X	X	X	—	X	—	X	X	—	—	X	—	X	—	—	—	X	—	—	—	—	—	—	X	—	—
Belote and Ratner [8]	..	F	8	14	X	X	X	X	X†	X	X	X	X	X	?X	X	X	—	X	X	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—
Keefer and Felty [2d]	1	F	36	24	X	X	X	X	—	X	X	—	—	X	X	—	—	X	X	—	—	—	—	—	—	X	—	—	—	—	—	—	—	—	—
Mook, Weiss and Bromberg [2a]	1	F	32	24	X	X	X	X	—	X	X	X	X	X	X	X	—	—	—	—	—	—	—	—	—	X	—	—	X	—	—	—	—	—	—
Friedberg, Gross and Wallach [13]	1	F	24	36	X	X	X	X	X	X	X	X	X	X	—	X	X	X	—	X	—	X	—	—	—	—	—	—	—	X	—	—	—	—	—
	2	F	48	38	X	X	X	X	X	—	X	X	X	—	—	—	X	X	X	—	X	X	X	X	—	—	—	—	—	X	—	—	—	—	—
Tremaine [9]	1	F	19	42	X	X	X	X	X	X	X	X	—	X	X	X	X	X	—	—	—	—	—	—	—	—	—	—	—	X	X	—	—	—	—
Rose and Goldberg [2c]	3	F	25	48	X	X	X	X	X	X	—	—	X	X	X	—	—	X	X	—	—	—	—	—	X	—	X	—	X	—	—	—	—	—	—
Total (17 cases)					17	17	17	15	15	13	13	12	12	10	10	9	9	9	8	6	6	5	5	5	4	4	3	3	3	3	2	2	2	0	0	0
Reifenstein, Reifenstein and Reifenstein	..	F	26	27	X	X	X	X	X	X	X	X	—	X	X	X	X	—	X	X	—	X	X	—	—	X	—	—	—	—	—	—	—	X	X	X
Total (18 cases)					18	18	18	16	16	14	14	13	12	11	11	10	10	9	9	7	6	6	6	5	4	5	3	3	3	3	2	2	2	1	1	1

* The reports of 17 of the cases were collected from the literature, and 1 case is reported in the present paper.
† Slight.

COMMENT

The accompanying tabulation of the essential features in the 17 selected cases revealed that every patient exhibited articular manifestations and pleuritis; all but 4 pericarditis, pneumonia or some erythema, and all but 5, peritonitis or endocarditis. Slightly more than half had nephritis or more or less diffuse arteritis. Other findings were too varied to be of possible diagnostic value. There seemed to be no one pathologic process which could be demonstrated as responsible for the widespread lesions. On the contrary, the impression was gained from the bronchopneumonia, diffuse congestion and degeneration that the majority of the acute lesions were the result of terminal infection occurring after some unknown process had damaged the endothelial tissues, heart, kidneys or other organs, perhaps rendering them more susceptible to terminal sepsis. It is possible also that some of the pathologic processes that occurred during the prolonged course of many of the cases subsided with little or no residual evidence to be found post mortem.

Our patient was observed for twenty-four days after the diagnosis of "diffuse peripheral vascular disease associated with lupus erythematosus and glomerulonephritis" was made, during which time extensive studies failed to reveal any etiologic factor. It is interesting to note the marked increase in the severity of the cutaneous lesions and of the state of the illness following exposure to sunlight. Such phenomena have been recorded in other cases.[28] In the case presented, bacteria were demonstrated in four instances: (1) an increased number of hemolytic streptococci in the throat, (2) Staph. aureus in the furuncle on the buttock, (3) nonvirulent diphtheria bacilli in the nose and (4) bacilli in the old caseating tubercle in the lungs. There was no evidence of widespread tuberculosis, which makes it difficult to conceive of the tubercle bacilli as responsible for the clinical picture. Tuberculosis has been suggested as the cause of lupus erythematosus, but recently there has been a tendency to minimize the finding of tubercle bacilli in these cases.[29] It seems reasonable to consider the tubercle in the case described as incidental and to look on the other bacteria present as secondary invaders. Nevertheless, infection with an unknown organism or organisms is a plausible explanation for a majority of the clinical signs and pathologic features. The involvement of the meninges is consistent with the apparent predisposition of the symptom complex to involve the serous membranes. Other abnormalities, such as the acute pancreatitis, the elevated metabolic rate and the low calcium and cholesterol levels of the blood, rendered the diagnostic problem all the more baffling.

28. Mook, Weiss and Bromberg.[2a] Rose and Goldberg.[2c] Tremaine.[9]

29. O'Leary, P. A.: Disseminated Lupus Erythematosus, Minnesota Med. **17**:637 (Nov.) 1934.

A symptom complex therefore presents itself which has no definite diagnostic criteria, no known etiologic factor and no single name by which it is designated. Most of the names by which it has been described are objectionable because they directly or by connotation emphasize certain features which have not been found to be universally present. This hampers the conception of the symptom complex as a possible unity and impedes progress toward a better understanding of the syndrome. To obviate this difficulty it is suggested that similar cases in the future be considered as a group, so that their various peculiarities may be given equal consideration but not undue prominence.

SUMMARY

The medical literature contains descriptions of a variable symptom complex which has all or many of the following features: prolonged fever, polyarthritis, polyserositis, endocarditis, erythematous cutaneous lesions, nephritis, anemia and a remittent cachectic course, with a fatal termination months to several years after the onset.

Reports of 17 such cases, with postmortem examinations, collected from the literature were analyzed. No definite diagnostic criteria could be adduced, although every patient exhibited articular manifestations and pleuritis; all but 4, pericarditis, pneumonia or some erythema, and all but 5 peritonitis or endocarditis. Slightly more than half had nephritis or more or less diffuse arteritis. Other findings were too varied to be of possible diagnostic value.

An additional case of our own, with postmortem data, is reported in detail. This patient showed most of the features that have been mentioned and also adhesive meningitis, acute pancreatitis, an elevated basal metabolic rate, lowered levels of calcium and cholesterol in the blood and hyperplasia of the bone marrow, which have not been previously described. Extensive studies gave no clue to the etiologic agent.

It is suggested that in the future similar ill defined conditions be considered as a group, in order that clarification may be aided.

NOTE.—Since this paper was submitted, reports of several additional cases have been published which come within the scope of this symptom complex. The first patient [30] was a woman aged 29 years. Her illness, of approximately sixteen months' duration, was characterized by weakness, loss of weight, cough, arthralgia and cutaneous lesions; by a purpuric tendency which was only temporarily ameliorated by splenectomy, and by terminal myocardial failure, lymphadenopathy, pneumonia and nephritis. Pathologic examination disclosed in almost every organ multiple arterial lesions which were said by Dr. Tracy B. Mallory

30. Acute Disseminated Lupus Erythematosus; Periarteritis Nodosa, Cabot Case 24201, New England J. Med. **218**:838 (May 19) 1938.

to be typical of periarteritis nodosa. However, Dr. Soma Weiss and several other clinicians contended that the clinical diagnosis should have been acute disseminated lupus erythematosus. The reader is referred to the excellent discussion of this case.

The second patient,[31] a girl of 12 years, exhibited during the four month course of her illness remittent fever, pyuria and anemia, with terminal myocardial failure, bronchopneumonia, pleural and pericardial effusions, cutaneous facial eruption and convulsions. Necropsy revealed hydropericardium, bronchopneumonia, hemolytic streptococcic empyema and septicemia and some embolic nephritis. Vascular lesions were not prominent. This case is of interest in that the clinical and pathologic diagnosis was acute disseminated lupus erythematosus, although cutaneous lesions were absent until three days ante mortem. In the discussion, reference was made to 15 cases reported from the Massachusetts General Hospital in which no constant lesion was observed post mortem.

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31. Acute Disseminated Lupus Erythematosus; Hydropericardium, Cabot Case 24341, New England J. Med. **219**:273 (Aug. 25) 1938.

MENINGOCOCCIC SEPTICEMIA

REPORT OF FIVE NEW CASES

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Meningococcic septicemia can no longer be regarded as a rare disease. Its recognition has been increasingly frequent since Gwyn, in 1898, demonstrated meningococci in the blood stream and since the report of Salomon,[1] in 1902, of meningococcic septicemia which persisted for eight weeks. The disease may be divided into the acute fulminating and the chronic septicemic type, the latter with various metastatic lesions and with or without meningitis.

Acute fulminating meningococcic septicemia is invariably fatal. Cases have been reported [2] in which the patient died a few hours after the onset, with an extensive purpuric rash, hematemesis and tarry stools. As in other fulminating infections, some patients [3] have shown massive hemorrhage into the adrenals. These acute attacks are characterized by their abrupt onset, with chills and high fever, rapid progression, purpura and massive hemorrhage into many organs. There is no effective treatment.

Chronic meningococcic septicemia is observed more frequently. It is characterized by headache, purpuric cutaneous rash, arthropathy of greater or lesser severity and fever, which may resemble that of tertian or quartan malaria and in any event is frequently of the "picket fence" variety, with frequent regular chills. There is moderate leukocytosis.

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1. Salomon, H.: Ueber Meningokokkenseptikame, Berl. klin. Wchnschr. **39**: 1045, 1902.

2. Middleton, R., and Duane, W.: Fulminating Meningococcus Septicemia Without Meningitis, Am. J. M. Sc. **177**:648, 1929. Burton, J. A. G., and Chalmers, D. K. M.: Purpura as a Sole Sign in a Case of Meningococcal Septicemia, Lancet **1**:296, 1930.

3. Foucar, F. H.: Acute Fulminating Meningococcus Infection with Bilateral Capillary Hemorrhage of the Adrenals as the Most Striking Gross Pathologic Lesions: A Case Report, Ann. Int. Med. **9**:1736, 1936. Boone, J. T., and Hall, W. W.: Meningococcal Septicemia with Report of a Case Showing Organisms in the Direct Blood Smear, U. S. Nav. M. Bull. **33**:446, 1935.

The spleen may or may not be palpable. Numerous authors [4] have commented on the fact that positive blood cultures may not be obtained until after the third week and have stressed the necessity of employing mediums enriched with ascitic fluid or blood. The duration of the disease may be several months, cases in which it lasted three,[5] four,[6] five,[7] seven [8] or eight [9] months having been reported. Spontaneous recovery frequently occurs. Cases [10] in which terminal meningitis followed a long period of septicemia have been observed.

The less common manifestations of chronic meningococcic septicemia include involvement of many different organs. Acute and subacute meningococcic endocarditis have been reported. Gwyn [11] reported a patient with an eight month history of subacute bacterial endocarditis, proved at autopsy. Herrick,[12] in 31 autopsies, observed acute tricuspid endocarditis once, and other authors [13] have reported vegetative and ulcerative endocarditis. Myocarditis, with lesions resembling those of rheumatic fever, also has been reported.[14] Fibrinopurulent and seropurulent pericarditis are known to occur.[12]

Meningococcic abscess of the sphenoid, frontal or ethmoid sinuses [15] has been reported. In Gardiner's case [16] metastatic iridochoroiditis

4. (*a*) Appelbaum, E.: Chronic Meningococcus Septicemia, Am. J. M. Sc. **193**:96, 1937. (*b*) Carbonell, A., and Campbell, E. P.: Prolonged Meningococcemia: Report of Three Cases, Arch. Int. Med. **61**:646 (April) 1938.

5. Pontano, T., and Trenti, E.: La setticemia meningococcica, Policlinico (sez. med.) **29**:3, 1922.

6. Netter, A.: Fièvre intermittente se prolongeant cent deux jours: Nature meningococcique soupçonnée, Bull. Soc. méd. d. hôp. de Paris **47**:46, 1923.

7. Graves, W. R.; Dulaney, A. D., and Michelson, I. D.: Chronic Meningococcemia, J. A. M. A. **92**:1923 (June 8) 1929.

8. Dock, W.: Intermittent Fever of Seven Months' Duration Due to Meningococcemia, J. A. M. A. **83**:31 (July 5) 1924.

9. Goundry, F. W., and Phalen, T. H.: Meningococcemia Without Meningitis, New York State J. Med. **37**:491, 1937.

10. Vesell, H., and Barsky, J.: Chronic Meningococcus Septicemia, Am. J. M. Sc. **179**:589, 1930. Gutland, G. L., and Logan, W. R.: Prolonged Meningococcemia with Terminal Meningitis, Brit. M. J. **1**:687, 1925.

11. Gwyn, N. B.: Subacute Meningococcal Endocarditis, Arch. Int. Med. **48**: 1110 (Dec.) 1931.

12. Herrick, W. W.: The Intravenous Serum Treatment of Epidemic Cerebrospinal Meningitis, Arch. Int. Med. **21**:541 (April) 1918.

13. (*a*) McMahon, H. E., and Burkhardt, E. A.: Meningococcic Endocarditis, Am. J. Path. **5**:197, 1929. (*b*) Rhoads, C. P.: Vegetative Endocarditis Due to Meningococcus, ibid. **3**:623, 1927.

14. Saphir, O.: Meningococcus Myocarditis, Am. J. Path. **12**:677, 1936. Rhoads.[13b]

15. Herrick, W. W.: Extrameningeal Meningococcic Infections, Arch. Int. Med. **23**:409 (April) 1919.

16. Gardiner, A. W.: A Case of Generalized Meningococcus Infection, Brit. M. J. **2**:1176, 1928.

developed, resulting in blindness. Epididymitis [4a] and empyema [15] also have been observed.

Some arthropathy appears at one time or another during the course in nearly every case, varying from mild fleeting pain in a joint to actual destruction of bone. Suppurative arthritis, however, is uncommon. Gardiner [16] reported suppurative arthritis of a knee joint in 1 case, from which meningococci were cultured, and Dock,[8] reviewing the literature in 1924, found only 3 instances of suppurative arthritis.

Five cases of chronic meningococcic septicemia have been observed at the Lakeside Hospital during the last eleven years. The unusual features of each will be discussed after its presentation.

REPORT OF CASES

CASE 1.—M. H., a 25 year old woman, entered the medical service of the Lakeside Hospital on July 21, 1935, because of "rheumatism," red rash over the body and drowsiness progressing to coma. She was known to be diabetic. Ten days before admission a "sore throat" had developed, accompanied by pain and swelling of the wrists and knees. Three days before admission a red rash had appeared over the body, especially on the chest, abdomen and back. She became drowsy and eventually comatose. There was no previous history suggestive of rheumatic fever.

Physical examination showed a temperature of 40.2 C. (104.4 F.), a pulse rate of 140, a respiratory rate of 32 and a blood pressure of 122 systolic and 68 diastolic. The patient was comatose. Over the chest, abdomen and back and to a lesser extent over the extremities was a dull red, macular, purpuric eruption, each macule measuring about 2 mm. in diameter. None were confluent. The tongue was red and swollen. The breath had a strong odor of acetone. The spleen was not palpable. Both knees, both elbows and the left wrist were swollen, red, tender and painful on motion. Over the dorsal aspect of the left wrist was a fluctuant mass, 5 cm. in diameter. Neurologic examination gave completely negative results.

Laboratory Findings.—The white cell count of the blood was 17,350, with a slight shift to the left; the red cell count, 3,260,000, with 70 per cent hemoglobin (Sahli). The sugar content was 444 mg. per hundred cubic centimeters. The carbon dioxide-combining power was 17.8 volumes per cent. The urine showed acetone (4 plus) and diacetic acid, with 2.5 per cent sugar.

Course in the Hospital.—Vigorous treatment with insulin and parenteral fluids brought the diabetes under control. High fever of the septicemic type continued, the temperature rising to 41.2 C. (106.2 F.). On the second day the subcutaneous abscess over the left wrist was incised, and several ounces of thick yellow pus was obtained. Culture yielded organisms which fermented dextrose, lactose and maltose and were agglutinated by known antimeningococcus serum in a dilution of 1:640. Blood culture in brain broth yielded no definite growth, but a few gram-negative organisms were recovered, which failed to grow after transfer to a blood agar plate. Subsequent blood cultures on brain broth, made on the third, the fourth, the fifth and the ninth day, were negative, although high fever continued. At this time the left ear began to discharge a thin, brown pus. The patient was given intravenously 10,000 units of meningococcus antitoxin (Parke-Davis) on the twelfth day and 20,000 units on each of the following

days through the sixteenth, a total of 90,000 units. This therapy had no effect, and the temperature frequently exceeded 40 C. (104 F.). Because of rapidly progressive anemia, the patient received several blood transfusions. On the thirty-fifth day a fluctuant area over the left scapula yielded 70 cc. of yellow pus, from which organisms were cultured which agglutinated with antimeningococcus serum in a dilution of 1:2,560. On the fifty-seventh day a red, fluctuant, swollen area on the right thigh was aspirated and 10 cc. of yellow pus obtained, which yielded only Staphylococcus albus on culture.

On the sixty-first day the left knee became swollen and fluctuant; seropurulent material obtained by aspiration yielded meningococci on culture, which were agglutinated by antimeningococcus serum (Lilly) in a dilution of 1:640. At the same time, roentgen examination of the second right metacarpal phalangeal joint revealed a destructive lesion. After the one hundred and eighth day the patient was afebrile. Strength and mobility of the left leg and right index finger returned. The abscesses over the left scapula, left wrist and right thigh healed readily after surgical incision. The patient was discharged on the two hundred and nineteenth day, at which time she could stand and take a few steps alone. The diabetes was well controlled.

Follow-Up Report.—A year and nine months after discharge the patient was in good health. She walked normally and had only occasional stiffness in the left knee.

This is a case of chronic meningococcic septicemia lasting about four months. Although blood cultures were consistently negative, except in a single doubtful instance, the presence of septicemia cannot be questioned, because of the ease with which meningococci were recovered from the various widely disseminated abscesses. The unusual feature is the presence of suppurative arthritis of a knee joint and destructive (?) suppurative arthritis of a metacarpophalangeal joint. There were three large subcutaneous abscesses, from two of which meningococci were recovered. Treatment with the meningococcus antitoxin originated by Ferry [17] was without demonstrable effect. Antimeningococcus serum was not administered. Spontaneous recovery occurred after about four months of the disease.

CASE 2.—I. T., a 36 year old Russian Jewess, entered Lakeside Hospital on Dec. 12, 1929, complaining of coldness and generalized pain, especially severe in the feet, of three months' duration. She stated that she had had similar attacks about once every three years for the twelve years preceding. Twelve years before she had been in another hospital for six weeks. Since then she had had three attacks characterized by fever, "spots" on the body, headache and malaise. All previous attacks had been preceded by a cold in the head with nasal discharge

17. Ferry, N. S., and Steele, A.: Active Immunization with Meningococcus Toxin, J. A. M. A. **104**:983 (March 23) 1935. Ferry, N. S.: Meningococcus Antitoxin: I. Prophylactic Therapeutic Tests on Guinea Pigs, J. Immunol. **23**: 315, 1932; II. Therapeutic Tests on Monkeys, ibid. **23**:325, 1932; III. Further Tests on Monkeys, ibid. **26**:133, 1934; IV. Further Tests on Guinea Pigs and Rabbits, ibid. **26**:143, 1934. Hoyne, A. L.: Treatment of Meningococcic Meningitis Without Intraspinal Therapy, Nebraska M. J. **21**:321, 1936.

and cough. The present illness had begun three months before admission, with a feeling of chilliness, pain in the feet, shaking chills and sweats. She had lost 40 pounds (18.1 Kg.).

Physical examination showed marked enlargement of the liver; the spleen and right kidney were palpable. Over the body were multiple red papular lesions.

Laboratory Findings.—The urine showed albumin and a few pus cells. The white cell count of the blood varied between 16,000 and 8,000; the red cell count was 3,800,000, with 65 per cent hemoglobin (Sahli). The Wassermann reaction was negative. Blood cultures taken on brain broth on the eleventh, the twenty-first and the thirtieth day in the hospital yielded meningococci which agglutinated with Parke-Davis antimeningococcus serum in a dilution of 1 : 1,600. The organism isolated from the blood stream was not agglutinated by the patient's own serum. The spinal fluid was normal.

Course in the Hospital.—For the first eighteen days the patient had daily chills at the same hour each day, the temperature rising to 40 C. with regularity. Chills and fever then became less regular. From the thirty-fourth to the thirty-ninth day she received 350 cc. of antimeningococcus serum intravenously. After this time the fever was less marked, and after the sixtieth day the temperature was normal. Numerous blood cultures taken after the institution of serum therapy were negative, and the patient was discharged.

Readmission.—She was readmitted nearly two years later, on Oct. 30, 1931. Since leaving the hospital she had continued to be weak and had become fatigued easily. A year before the second admission she had begun to cough and had vomited frequently and also had frequent epistaxes.

Physical examination again showed marked enlargement of the liver, now with prominent superficial veins on the abdomen. Moderate jaundice was present. The spleen was enlarged.

Laboratory Findings.—The red cell count of the blood was 2,470,000, with 50 per cent hemoglobin (Sahli); the white cell count, from 13,400 to 9,800. The icterus index was 27. Blood culture on the fourteenth day in the hospital yielded meningococci.

Course in the Hospital.—The temperature varied irregularly from 37.5 to 40.2 C. (99.5 to 104.4 F.). Bilateral bronchopneumonia developed on the fourteenth day in the hospital, and the patient died on the twenty-first day. She had received 100 cc. of antimeningococcus serum intravenously two days before death.

Autopsy.—The important pathologic diagnoses were cirrhosis of the liver, nephrosclerosis, bronchopneumonia and hemorrhage into the cerebellum. There is no record in the protocol of the autopsy of postmortem bacteriologic studies.

The patient had a history strongly suggestive of recurrent attacks of meningococcic septicemia over fourteen years, with six attacks during that time. The last two, two years apart, were observed in Lakeside Hospital, and the meningococcus was recovered from the blood stream on both occasions and from the nose and throat on the first occasion. It appears that the antimeningococcus serum given on the first admission was of value in shortening that attack, but there was recurrence two years later. On the last admission antiserum therapy was not instituted until the patient was moribund, and she died of causes probably unrelated to the meningococcic septicemia. There was no evidence of meningitis

at any time, and the spinal fluid was consistently normal. The patient had regular daily chills and a "picket fence" type of fever on the first admission, but on the second admission the fever was irregular, and there were no chills.

CASE 3.—A. O., a 42 year old white man, was admitted to Lakeside Hospital on July 20, 1930, stating that six days before admission he had experienced marked malaise, with shaking chills and constant pain in the lower extremities. On the following day a diffuse red rash had appeared. He continued to be weak and drowsy, perspired and had pain in the legs.

Physical examination showed a diffuse maculopapular red rash involving the entire body except the scalp, soles and palms. A few of the lesions were pustular, and many were definitely purpuric.

Laboratory Findings.—The red cell count of the blood was 4,400,000, with 66 per cent hemoglobin (Sahli); the white cell count, 20,000 to 10,000. Repeated blood cultures during the first four months yielded meningococci agglutinating with antimeningococcus serum (Lilly and Lederle), in dilutions of 1:640. The spinal fluid was normal.

Course in the Hospital.—During the first five months fever was persistent, irregular and sometimes septic. At the end of this time the patient received a blood transfusion, after which the temperature gradually subsided. A spontaneous pneumothorax occurred on the left but subsequently disappeared. An autogenous meningococcus vaccine was prepared and was administered in small doses over a period of two weeks. During the last two of his six months' stay in the hospital the patient's improvement was gradual, with fewer recurrences of the purpuric rash. At the end of six months he was discharged symptom free and had not had a positive blood culture for two months.

Readmission.—He was readmitted five years later, on March 1, 1935, complaining of frequent sharp, severe pain low in the back, associated with bouts of fever lasting two to three days. On three occasions he had observed a few scattered red lesions, the size of a pinhead, mostly on the legs but occasionally on the trunk. Physical examination showed no abnormality. Eight blood cultures yielded no growth. The temperature was normal; the patient was asymptomatic and was discharged without subjective or objective findings after ten days. No diagnosis was established. Unfortunately he was followed no further.

This is a typical case of chronic meningococcic septicemia lasting about four months. The patient was already improving when autogenous vaccine was given. Whether or not he experienced recurrent attacks during the five years between the first and second hospital admissions is impossible to say with certainty. Convalescence seemed to be accelerated after a blood transfusion.

CASE 4.—J. J. S., a 19 year old white youth, was admitted to Lakeside Hospital on July 2, 1937, complaining of chills and fever of five weeks' duration. At the onset there was pain in the small toe of the right foot. No rash appeared on the skin at any time.

Physical examination showed no abnormality except a harsh systolic murmur at the apex of the heart. There was no antecedent history of rheumatic fever or heart disease.

Laboratory Findings.—The red cell count of the blood was 4,570,000, with 74 per cent hemoglobin (Sahli); the white cell count was 17,400. Three blood cultures were positive for meningococci, but only after fourteen days' incubation.

Course in the Hospital.—There were severe shaking chills daily, with elevation of temperature to over 40 C. (104 F.) each time for the first eighteen days. Severe anemia developed, and petechiae appeared in the palate and conjunctivas. Red blood cells were present in the urine. The systolic murmur became louder and rougher. The patient experienced pain in the left side of the chest, and this was followed by hemoptysis. He was given 140,000 units of Parke-Davis meningococcus antitoxin intravenously and large doses of sulfanilamide. A blood transfusion of 500 cc. was given on the seventeenth day. After the eighteenth day there were no more chills, and the temperature became irregular, not exceeding 38.5 C. (101.3 F.). However, he became worse rapidly and died on the twenty-third day in the hospital. Permission for autopsy was refused.

This case is an instance of meningococcic septicemia progressing to a fatal termination in eight weeks. Clinically the patient exhibited signs of endocarditis, as evidenced by a rough, progressively louder systolic murmur, with petechiae and probably infarcts of the kidneys and left lung. No signs of meningeal irritation were present at any time. Meningococcus antitoxin and sulfanilamide had no effect, although they were not used until late in the course of the disease. It is interesting that after blood transfusion there were no further chills and the fever was considerably decreased, whereas before the transfusion severe chills and high fever occurred regularly twice a day. Although not proved by autopsy, a diagnosis of acute meningococcic endocarditis with multiple embolic phenomena seems justified.

CASE 5.—T. A., a 32 year old white man, was admitted to Lakeside Hospital on Dec. 17, 1935, complaining of repeated chills for two weeks. Four months before admission he had begun to have migratory transient pains in the joints and muscles, with redness and swelling of many joints. At times his temperature had reached 38.3 C. (100.9 F.). Two weeks before admission he had had a shaking chill lasting fifteen minutes. Since that time he had had two or three shaking chills daily, associated with high fever.

Physical examination showed a pale, obviously ill man with cervical, axillary, epitrochlear and inguinal lymphadenopathy. The heart was normal. No murmurs were present. The spleen was palpable.

Laboratory Findings.—The urine contained albumin and red cells. The red cell count of the blood was 2,500,000, with 72 per cent hemoglobin (Sahli); the white cell count, 12,000 to 19,000. Blood cultures on brain broth on the tenth, the twenty-first, the twenty-second, the twenty-third and the twenty-fifth day in the hospital yielded organisms subsequently proved to be meningococci and agglutinated by antimeningococcus serum (Lilly and Lederle) in dilutions of 1:1,280. The gonococcus complement fixation test was positive. Roentgen examination revealed bilateral polycystic kidneys.

Course in the Hospital.—The patient had a severe shaking chill with elevation of temperature to 40 or 41 C. (104 or 105.8 F.) daily. He received a daily blood transfusion on the thirteenth, the fourteenth and the fifteenth day, because of progressive anemia. Because the organisms cultured from the blood were first

believed to be streptococci, he received 20 cc. of antistreptococcus serum on the sixteenth and the eighteenth day. Later, because of the positive gonococcus fixation test, he received two injections of gonococcus filtrate intradermally. The identification of the organism was not completed until after the death of the patient; hence he was not treated with antimeningococcus serum. On the twentieth day a rough systolic and diastolic murmur appeared at the aortic area. These remained constant during the remainder of the course in the hospital. Petechiae were not observed at any time. On the twenty-seventh day the patient had a generalized convulsion and died. Permission for autopsy was not obtained.

While the diagnosis was not proved at autopsy, this was a case of chronic meningococcic septicemia apparently terminating with acute meningococcic endocarditis of the aortic valve. The temperature was of the "picket fence" type, with daily severe chills and high fever. Three blood transfusions, of 300, 400 and 500 cc., were without observable beneficial effect.

COMMENT

Because of the varied manifestations of infection with the meningococcus, it has been proposed [2] that the term "epidemic meningitis" should be abandoned and, further, that meningeal involvement should be considered as only one, albeit the most obvious, manifestation of meningococcic infection. Herrick [18] suggested that meningococcic infection occurs in three stages: (1) acute infection of the upper part of the respiratory tract, (2) septicemia and (3) metastatic localization in various sites, including the meninges, joints, heart, lungs, pericardium and skin. Friedemann and Deicher [19] expressed the opinion that many catarrhal diseases of the respiratory tract are frequently due to unrecognized meningococcic infection.

In the cases here reviewed, 1 patient displayed purulent arthritis, and in addition numerous large subcutaneous abscesses. The presence of diabetes may have made this patient more susceptible to the formation of abscesses. Another of the patients had a history suggesting attacks of meningococcic septicemia over fourteen years, with two proved attacks two years apart. Two other patients gave good clinical evidence of acute endocarditis as a terminal event. These instances emphasize the variety of manifestations and the possible long duration of the disease.

The difficulty in culturing organisms is also demonstrated. Definitely positive blood cultures were never obtained in case 1, although the ease with which the organism was isolated from the numerous foci makes it obvious that septicemia did exist, at least intermittently. In case 4 blood

18. Herrick, W. W.: Meningococcus Infections Including Cerebrospinal Fever, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1938, vol. 5, pt. 1, chap. 4, p. 77.

19. Friedemann, U., and Deicher, H.: Ueber die Lenta-Form der Meningokokkensepsis, Deutsche med. Wchnschr. **52**:733, 1926.

cultures became positive only after fourteen days' incubation on enriched mediums. The necessity for prolonged incubation and the use of enriched mediums is further emphasized.

Effectiveness of specific treatment is not indisputable. It is generally agreed,[20] however, that the course of the disease is probably shortened by the use of specific antimeningococcus serum. One of the patients, although receiving adequate doses of meningococcus antitoxin, appeared to derive no benefit from the treatment. Carbonell and Campbell [4b] recently reported 3 cases of meningococcic septicemia and concluded that the most effective treatment is the use of the proper antimeningococcus serum in conjunction with sulfanilamide.

SUMMARY

Meningococcic septicemia, with its various metastatic lesions, is being recognized with increasing frequency.

There are an acute fulminating and a chronic type. The acute fulminating condition is invariably fatal. The chronic condition may last many months, and recovery is frequently spontaneous.

Five cases of the chronic type are reported. One patient had purulent arthritis; 1 had a history suggestive of attacks of the disease over fourteen years, and 2 presented clinical evidence of acute endocarditis.

Meningitis should be regarded as only one metastatic lesion of meningococcic septicemia. Lesions of the endocardium, myocardium, pericardium, lungs, sinuses, eyes, epididymis and joints also occur.

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20. Bloedorn, W. A.: Meningococcus Septicemia, Am. J. M. Sc. **162**:881, 1921. Richter, A. B.: Meningococcemia, J. A. M. A. **102**:2012 (June 16) 1934. Marlow, F. W.: Meningococcemia, ibid. **92**:619 (Feb. 23) 1929. Clarke, F. B.: Chronic Meningococcemia, California & West. Med. **34**:361, 1931. Le Bourdellès, B.: De la fréquence de la méningococcie à forme purpurique, Presse méd. **33**: 660, 1925. Appelbaum.[4a] Goundry and Phalen.[9]

IS IRON EXCRETED BY THE GASTROINTESTINAL TRACT OF THE DOG?

A HISTOLOGIC STUDY

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The problem of the absorption and excretion of iron by the gastrointestinal tract remains baffling in spite of studies by numerous investigators during many years. The conclusions of many workers that iron is absorbed by the small and excreted by the large intestine have not been confirmed by recent investigations. Wallbach,[1] after repeating on mice the experiments of Hochhaus and Quincke, came to the conclusion that there is no morphologic criterion for the determination of whether iron is being absorbed or excreted, since the morphologic appearance of iron in the intestine is the same in the two instances. M'Gowan,[2] from a study of the literature and from observations on fowls suffering from hemolytic anemia, came to the conclusion that there is apparently "no justification for the statements current regarding the movements of iron in the body, namely that while absorption takes place solely from the duodenum, excretion is limited to the large intestine." A review of the literature on iron metabolism by Heath and Patek[3] indicated that excretion of iron by the bowel is probably extremely small, and the clinical observations of these authors confirmed

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1. Wallbach, G.: Experimentelle Untersuchungen über die Verteilung und Ablagerung einiger medikamentöser Eisenpräparate, Ztschr. f. d. ges. exper. Med. **75**:353, 1931.

2. M'Gowan, J. P.: The Absorption and Excretion of Iron by the Intestines and the Nutritional and Therapeutic Value of Its Salts, Edinburgh M. J. **37**:85, 1930.

3. Heath, C. W., and Patek, A. J.: The Anemia of Iron Deficiency, Medicine **16**:267, 1937.

the impression that, whereas gastrointestinal abnormality interfering with absorption of iron from the food may condition the development of anemia when there is rapid growth or excessive loss of blood, excretion of iron must play only a small part. Reimann, Fritsch and Schick,[4] Fowler and Barer [5] and Brock and Hunter [6] have recently found that when iron in large doses is given orally to patients with hypochromic anemia there is a much greater retention of iron than can be accounted for by the amount required for the formation of hemoglobin. This work has led to new speculations regarding the intrinsic metabolism of iron and has indicated the great capacity of the body to absorb and store iron and its relative inability to excrete iron. McCance and Widdowson [7] concluded that the power of the intestine to excrete iron has been greatly exaggerated. This conclusion has been confirmed by direct experimentation. Fowler and Barer [8] were unable to demonstrate an increased excretion of iron in the feces after the parenteral administration of iron to man. Henriques and Roland [9] observed that after the intravenous injection of iron citrate and iron lactate there was a small increase of iron in the urine but no increase in the feces. Henriques and Roche [10] also observed that there was no increase of iron in the isolated large bowel when iron lactate was given orally. Nicolaysen [11] recorded no increase of iron in the large or small bowel of the dog after the injection of iron. Numerous observations indicate that the bile contains only traces of iron even after the administration of iron orally and parenterally.

Clinically and experimentally, therefore, it appears that the excretion of iron by the gastrointestinal tract is an unimportant matter, and it may even be doubted that excretion in the ordinary sense takes place

4. Reimann, F.; Fritsch, F., and Schick, K.: Eisenbilanzversuche bei Gesunden und bei Anämischen, Ztschr. f. klin. Med. **131**:1, 1936.

5. Fowler, W. M., and Barer, A. P.: Iron Retention Following Use of Ferric Ammonium Citrate in Hypochromic Anemia, J. A. M. A. **104**:144 (Jan. 12) 1935.

6. Brock, J. F., and Hunter, D.: The Fate of Large Doses of Iron Administered by Mouth, Quart. J. Med. **6**:5, 1937.

7. McCance, R. A., and Widdowson, E. M.: Absorption and Excretion of Iron, Lancet **2**:680, 1937.

8. Fowler, W. M., and Barer, A. P.: Retention and Utilization of Parenterally Administered Iron, Arch. Int. Med. **60**:967 (Dec.) 1937.

9. Henriques, V., and Roland, H.: Zur Frage des Eisenstoffwechsels, Biochem. Ztschr. **201**:479, 1928.

10. Henriques, V., and Roche, A.: Sur l'elimination intestinale du fer chez le chien, Bull. Soc. chim. biol. **12**:404, 1930.

11. Nicolaysen, R.: Untersuchungen über die Eisenausscheidung im Darmkanal bei Hunden: Beitrag zur Physiologie des Kolons, Skandinav. Arch. f. Physiol. **72**:126, 1935.

at all from this organ. The following work was undertaken in order to determine whether by repeated histologic study of the intestines of dogs significant evidence for the excretion of iron could be demonstrated.

EXPERIMENTAL METHOD

A 4 cm. section of the lower end of the colon was grafted with its blood supply intact to the abdominal wall by the colonic explant method of Drury, Florey and Florey.[12] This operation was performed on 4 dogs. The advantages of such a procedure are obvious. Repeated and frequent removal of material from the graft for histologic study is possible. The secretions of the graft can be collected and studied, at least qualitatively, for iron. The contents of the bowel are not in contact with the graft, so that the appearance of iron in histologic sections cannot be construed as indicating absorption of iron.

Iron was injected intramuscularly or intravenously daily or was given by mouth to these dogs and also to 2 normal dogs on which no operation had been done. Twenty to 100 mg. of metallic iron was given daily by the parenteral route, iron and ammonium citrates in 10 per cent solution being employed. On a few occasions iron hydroxide in colloidal solution containing 1 mg. of iron per cubic centimeter was employed for parenteral use. For oral use four to twelve tablets each containing 0.25 Gm. of ferrous sulfate were given daily. Iron in these doses was well tolerated. No attempt was made to control the diet of the dogs, which consisted of bread, milk and meat.

Small pieces of the graft were removed at frequent intervals. No anesthetic was necessary, and the wounds healed well without the application of antiseptics. At less frequent intervals the dogs were anesthetized with ether, the abdominal cavity was opened under aseptic precautions and small pieces of tissue were removed from the following organs: the liver, the spleen, the fundus of the stomach, the duodenum (7 cm. below the pancreatic duct), the lower portion of the ileum, the cecum and occasionally the colon. The wounds were sutured with silk, and the abdominal cavity was closed. After this operation a small piece of the graft and of the abdominal skin was removed. The tissues were placed in solution of formaldehyde U. S. P. (redistilled in glass) and in Zenker's solution. Tissues fixed in formaldehyde solution were stained for iron by the potassium ferrocyanide method, careful precautions being taken against iron contamination. Tissues fixed in Zenker's solution were stained with hematoxylin and eosin. At first 50 per cent alcohol was employed as a fixative agent, but it had no particular advantages over solution of formaldehyde.

In dogs 1, 2, 3 and 4 a graft of the colon on the abdominal wall was performed. The transplantation of the graft took place about six months prior to the present experiments. Dogs 5 and 6 had no graft. From 2 additional dogs specimens of tissue from the liver and spleen were taken to be stained for iron.

PROTOCOLS

Dog 1 (German shepherd).—The animal weighed 15.6 Kg. Colloidal iron hydroxide was injected intravenously daily, the dose commencing with 20 cc. and increasing gradually to 40 cc. on the seventh day. The injections were continued until the forty-first day. Tissue for biopsy was taken from the graft before the injection of iron and on the fourth, sixth, eighth, sixteenth, thirty-fifth and one

12. Drury, A. N.; Florey, H., and Florey, M. E.: The Vascular Reactions of the Colonic Mucosa of the Dog to Fright, J. Physiol. **68**:173, 1929.

hundredth days. Operation with removal of biopsy tissue from the internal abdominal organs and from the graft and skin was performed on the forty-first and one hundred and thirty-fifth days.

Dog 2 (Hound).—The animal weighed 14.3 Kg. Two cubic centimeters of solution of iron and ammonium citrates was injected intramuscularly daily for twenty-six days. Three cubic centimeters daily was injected from the one hundred and sixty-eighth to the two hundred and third day. Material for biopsy was taken from the graft twice before administration of iron and on the tenth, fifteenth, thirty-first and ninety-fourth days. Operation with removal of biopsy tissue from the internal organs and from the graft and skin was performed on the twenty-sixth, one hundred and thirty-fifth and two hundred and third days.

Dog 3 (Airedale).—The animal weighed 12.9 Kg. Ferrous sulfate (1 Gm. gradually increasing to 3 Gm. daily) was given for forty days. Intramuscular injection of iron and ammonium citrates was made daily in amounts of 2 to 3 cc. from the one hundred and eighty-first to the two hundred and sixteenth day. Tissue for biopsy was taken from the graft before administration of iron and on the third, fifth, seventh, sixteenth, thirty-sixth and one hundred and seventh days. Operation with removal of biopsy tissue from the internal organs and from the graft and skin was performed on the forty-first, one hundred and forty-fourth and two hundred and sixteenth days.

Dog 4 (Spaniel).—The animal weighed 12.7 Kg. Ferrous sulfate (1 Gm. gradually increasing to 3 Gm. daily) was given for forty-one days. Tissue for biopsy was removed from the graft before administration of iron and on the fourth, sixth, eighth, fourteenth and thirty-fourth days. On the forty-second day the dog died under ether anesthesia, before operation. Specimens from the internal organs and from the graft and skin were taken immediately.

Dog 5 (Mongrel).—The animal weighed 25 Kg. From 3 to 6 cc. of a solution of iron and ammonium citrates was injected intramuscularly daily for fifty-three days. Operation with removal of biopsy tissue from the internal organs and from the graft and skin was performed before the administration of iron and on the fifty-fourth day.

Dog 6 (Mongrel).—The animal weighed 10 Kg. From 3 to 6 cc. of a solution of iron and ammonium citrates was injected intramuscularly daily for forty-four days. Operation with removal of biopsy tissue from the internal organs and from the graft and skin was performed before the administration of iron and on the forty-fifth day.

COMMENT

Qualitative tests for iron were performed repeatedly on the mucus collected from the grafts of the first 4 dogs but gave consistently negative results. For these tests the following reagents were employed: ammonium sulfide, sulfanilic acid and ammonium sulfocyanate.

Microscopic examination of the sections of the graft which were first prepared with stock solution of formaldehyde as a fixative revealed appreciable amounts of iron deposited chiefly in the goblet cells of the mucosa but also throughout the connective tissue. It was soon apparent that this iron was artefactitious. It was present at times both before and after the administration of iron. When solution of formaldehyde and water which had been redistilled in glass were employed, iron within

the mucous cells was always absent. The following experiments also were made. Sections were made and mounted from paraffin blocks of biopsy material from the graft, which did not show iron in the mucous cells. These sections were placed in 1 per cent ferrous sulfate for five minutes, washed in running water for about three minutes and stained for iron. All sections thus prepared contained large amounts of iron deposited particularly within the epithelial cells and in the connective tissue between and beneath the glands. It therefore appears that iron demonstrated within the epithelial cells and much of that in the connective tissue was an artefact and came from small amounts of iron in the solution of formaldehyde and in the washing fluids. Iron was present similarly within the epithelial cells when a dressing soaked in a solution containing 1 per cent ferrous chloride and 10 per cent dextrose was placed on the graft for twenty-four hours. No further trouble with this kind of artefact was experienced when extreme precautions were taken against contamination with iron. This experience nevertheless demonstrates a possible source of serious error in the interpretation of results based on the histologic study of iron in tissues.

Since the observations failed to demonstrate any definite evidence of iron in the process of excretion by the bowel, they will be reported only briefly. As may be anticipated, the liver and spleen of each animal contained large deposits of iron after the administration of this metal orally and parenterally. After the largest amounts of iron had been given for a prolonged period, hemosiderin granules were seen in the preparations of tissue from the liver and spleen fixed in Zenker's solution. The iron appeared intracellularly within phagocytes of the spleen and Kupffer cells of the liver but also throughout the pulp of the spleen in large masses and within the parenchymal cells of the liver. In contrast to the liver and spleen, the various parts of the gastrointestinal tract contained only traces of iron, the small intestine containing almost none and the stomach, large intestine, graft and skin showing traces which appeared to be increased after iron was administered. The iron found in these organs was always scattered in the connective tissue of the mucosa and submucosa and was never found within the mucous cells. In the skin, iron was deposited in the corium. Frequently these minute collections of iron appeared to be intracellular. They were sometimes in close approximation to small blood vessels.

Although the traces of iron found within the wall of the stomach and large intestine may be considered to be in the process of excretion, they may with at least equal probability be stored iron. In appearance the iron resembles that found in the skin, which is without much question stored iron or iron in a stage of transportation. In these observations the largest deposits of iron were in the liver and spleen.

This iron was certainly stored, even though eventually it may have shifted its position and character. Since traces of iron similar to those seen in the stomach and large bowel were seen in the graft, it is certain that they were not in the process of absorption. A section of the kidney of dog 4 after administration of iron revealed large traces of iron, chiefly intracellularly in the connective tissue between the tubules. It seems reasonable to believe that this, too, was stored iron.

CONCLUSION

Histologic study of the gastrointestinal tract and of a colonic explant on the abdominal wall of the dog before and after the administration of iron revealed no evidence that iron can be observed in the process of excretion by these organs. It seems reasonable to believe that the traces of iron seen in the walls of the stomach and the large bowel were in a state of storage rather than of excretion. Such a conclusion confirms the recently advanced opinion that the excretion of iron by the bowel is extremely small.

Progress in Internal Medicine

BRIGHT'S DISEASE

A REVIEW OF RECENT LITERATURE

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In this field the most conspicuous investigative activities during the past year have been concerned with renal factors in hypertension, growing out of Goldblatt's work. Interest has been sustained in the nature of glomerulonephritis, in the renal disorders of pregnancy and in pyelonephritis. Studies of renal function have been concerned with intermediate steps in the formation of urine in health and in disease.

GLOMERULONEPHRITIS

Baehr [1] takes issue with those who would make a diagnosis of diffuse glomerulonephritis on the basis of urinary abnormalities alone or on the postmortem observation of diffuse glomerular changes in diseases, such as rheumatic fever, in which manifestations of nephritis are inconspicuous or lacking. Since glomerulonephritis must be considered a general vascular disease, of which the renal lesions are only a part, there should be evidence of extrarenal vascular damage to substantiate a diagnosis. He points out the rarity of gross clinical manifestations of glomerulonephritis in rheumatic fever as an argument that the diffuse glomerular changes previously described by Bell are not to be taken as evidence of true nephritis.

The opposite point of view is presented by Murphy and Rastetter,[2] who show that a considerable number of patients present themselves with chronic glomerulonephritis who have no knowledge of an acute phase of the disease. Furthermore, mild, subclinical forms of the disease are frequently observed, which present at first only urinary abnormalities, yet nevertheless progress to outspoken chronic glomerulonephritis. These facts are cited in support of Bell's view that innumerable transitions occur between subclinical and clinical glomerulonephritis. These are of great importance in establishing the links of evidence

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1. Baehr, G.: The Nature of Glomerulonephritis, Bull. New York Acad. Med. **14**:53 (Feb.) 1938.

2. Murphy, F. D., and Rastetter, J. W.: Acute Glomerulonephritis, with Special Reference to the Course and Prognosis: A Study of One Hundred and Fifty Cases, J. A. M. A. **111**:668 (Aug. 20) 1938.

between chronic glomerulonephritis and the less obvious etiologic factors in this disease.

Murphy and Rastetter [2] consider acute glomerulonephritis to exist if hematuria, albuminuria and cylindruria persist for a week, even if extrarenal vascular phenomena are lacking. Loeb [3] requires the persistence of these signs for ten to fourteen days and thinks it best to admit doubt if extrarenal vascular phenomena are lacking. He concludes that the percentage of cases of recovery and the proportion of cases in which the condition becomes chronic, as reported by different authors, vary because of the differences in criteria on which a diagnosis of acute nephritis is based.

Murphy and Rastetter [2] record the outcome of acute glomerulonephritis in 150 cases. Of the 150 patients, 105 were under 30 years of age. Of the latter, 50 per cent recovered, 40 per cent became chronically ill and 10 per cent died. Of the patients over 30 years of age, about 50 per cent recovered, 25 per cent became chronically ill and 25 per cent died. They remark that the disease may run its whole course without hypertension. Elevation of blood pressure was noted in only one third of the cases in which recovery occurred, in one half of the cases in which the disorder became chronic and in one third of the fatal cases.

The observations of Murphy and Rastetter have led them to the conclusion that persons in whom chronic nephritis develops, even years after an acute attack, have had continuous inflammation of the kidneys (prolonged latency) or chronic activity punctuated by remissions and exacerbations induced by attacks of infection of the upper respiratory tract. Baehr [1] also believes that patients who have had acute glomerulonephritis have suffered severe and permanent damage to the kidneys. Even though recovery seems to be complete for years, pregnancy or intercurrent infection may precipitate a recurrence. In cases of supposed recovery, arterial hypertension may develop insidiously.

Regarding the question of permanence of recovery in acute glomerulonephritis, Loeb, Lyttle, Seegal and Jost [4] report that in 8 of 10 cases in which the disorder was preceded by hemolytic streptococcic infection, healing occurred in from eight months to three years. Thereafter in each instance no recurrence of the nephritis was noted when intermittent hemolytic streptococcic infection occurred. In the 2 remaining cases transient urinary abnormalities were noted with intercurrent infection; however, in none of the 10 cases did the condition become chronic. Loeb [3] states that once the urinary picture has returned completely to

3. Loeb, R. F.: Clinical Aspects of Nephritis, Bull. New York Acad. Med. **14**:65 (Feb.) 1938.

4. Loeb, E. N.; Lyttle, J. D.; Seegal, D., and Jost, E. L.: On the Permanence of Recovery in Acute Glomerulonephritis, J. Clin. Investigation **17**:623 (Sept.) 1938.

normal, there is little danger of the development of chronic nephritis. He has observed many patients with this type of condition who have had recurrent infection of the upper respiratory tract which has not resulted in the reappearance of urinary abnormalities.

The importance of the erythrocyte sedimentation rate as an index of activity in glomerulonephritis is mentioned by Murphy and Rastetter,[2] who report that it is high in the acute stages and that it diminishes as healing occurs. The titer of antistreptolysins in the serum is shown by Lyttle, Seegal, Loeb and Jost [5] to be related to the severity, persistence and recurrence of hemolytic streptococcic infections. However, these observers were unable to find any significant correlation between the antistreptolysin titer and the severity or duration of acute nephritis or the tendency for chronic nephritis to develop.

Baehr [1] mentions the frequency of acute myocarditis in acute nephritis. Rubin and Rapoport [6] report 14 instances of acute myocardial involvement in 55 cases of acute nephritis, evidence of which was found in dyspnea, tachypnea, cough, enlargement of the heart, muffled heart tones, rapid rate, murmurs, gallop sounds, signs of congestive failure and abnormalities of the electrocardiogram. In all 55 cases the only deaths which occurred were from heart failure, which appeared to be precipitated by hypertension. In the treatment of these patients they recommend restriction of fluids and the use of a 50 per cent solution of magnesium sulfate, in doses of 0.2 cc. per kilogram of body weight, by intramuscular injection.

Langendorf and Pick [7] discuss the electrocardiogram in acute nephritis. The changes most frequently found were (*a*) flattening of the T wave in lead I or a peculiar bifid T wave in some cases; (*b*) discordant changes in the final deflections in lead III, the T wave becoming a large upright summit, and (*c*) reversal of direction of the normally negative T wave in lead IV, with an occasional bifid T_4. These changes differ from those accompanying occlusive lesions in the anterior wall of the left ventricle in that ST deviations do not occur, Q_1 does not develop and Q_4 does not disappear. Bifid T waves are not observed in cases of arterial occlusion.

Ehrström [8] reviews the evidence which connects glomerulonephritis, periarteritis and rheumatic arteritis with allergy, taking the view that

5. Lyttle, J. D.; Seegal, D.; Loeb, E. N., and Jost, E. L.: The Serum Antistreptolysin Titre in Acute Glomerulonephritis, J. Clin. Investigation **17**:631 (Sept.) 1938.

6. Rubin, M. I., and Rapoport, M.: Cardiac Complications of Acute Hemorrhagic Nephritis, Am. J. Dis. Child. **55**:244 (Feb.) 1938.

7. Langendorf, R., and Pick, A.: Elektrokardiogramm bei akuter Nephritis, Acta med. Scandinav. **94**:1 and 36, 1938.

8. Ehrström, M. C.: Irreversible, Allergic Reactions with Non-Bacterial Antigen, Acta med. Scandinav. **94**:346, 1938.

they are all irreversible reactions of an allergic nature, due in some cases to bacterial antigens and in other instances to food antigens. He describes a case in which signs of acute diffuse glomerulonephritis, manifested by hematuria, albuminuria, cylindruria and edema, developed with the eating of certain fruits by a patient with food allergy. The symptoms would disappear if the foods were withdrawn, and exacerbations could be induced by testing with food antigens.

The experimental glomerulonephritis produced by the use of nephrotoxic serum (Masugi-Smadel) has been studied by Ehrich, Wolf and Bartol.[9] These observers show that the structural and functional changes in this form of experimental nephritis in rabbits are the same as those of glomerulonephritis in human beings. In its pathogenesis the disease begins with a period of latency characterized by hyperemia of the glomeruli and in a number of cases by increased diuresis. In view of this finding the angiospastic theory of Volhard is untenable. Proliferation of glomerular cells is the typical lesion of the acute phase. Oliguria, marked proteinuria and diminished glomerular filtration (measured with cyanol) occur at the time when the glomerular changes are at their peak and are chiefly attributable to glomerular injury. In the acute phase excretion of azofuchsin I was not diminished except in 1 rabbit which at autopsy showed fatty changes in the tubules. Elsewhere these authors have shown that azofuchsin I is eliminated largely by tubular activity. Hence they conclude that in initial acute nephritis, the glomeruli and tubules may function independently of each other.

Hamori and Koranyi[10] have studied the influence of denervation of the kidneys on experimental glomerulonephritis (Masugi). They found that denervation of the kidneys of animals subjected to injections of nephrotoxin did nothing except prevent prealbuminuric retention of water. The subsequent development of Masugi nephritis and hypertension proceeded in the same way as in animals not subjected to denervation.

NEPHROSIS

Murphy, Warfield, Grill and Annis[11] discuss the controversial point as to whether true lipoid nephrosis exists as an entity distinct from glomerulonephritis. They report 9 cases which they regard as instances of genuine lipoid nephrosis. Two of the patients died, and careful histo-

9. Ehrich, W. E.; Wolf, R. E., and Bartol, G. M.: Acute Experimental Glomerular Nephritis in Rabbits: A Correlation of Morphological and Functional Changes, J. Exper. Med. **67**:769 (May) 1938.

10. Hamori, A., and Koranyi, A.: Der Einfluss der Entnervung der Nieren auf die Masugi-Nephritis, Ztschr. f. klin. Med. **133**:722, 1938.

11. Murphy, F. D.; Warfield, L. M.; Grill, J., and Annis, E. R.: Lipoid Nephrosis: A Study of Nine Patients with Special Reference to Those Observed Over a Long Period, Arch. Int. Med. **62**:355 (Sept.) 1938.

logic study of the kidneys at autopsy revealed no evidence of glomerular lesions. Six patients recovered, and 1 still remains under observation. They conclude that pure lipoid nephrosis is a rare disease but that it is an entity distinct from glomerulonephritis. They believe there is good reason to retain the distinction.

In a study of the intraocular pressure of an edematous patient with the nephrotic syndrome, Robertson [12] found no relation between the colloid osmotic pressure of the plasma and the intraocular pressure, which remained constant and normal through all variations in colloid osmotic pressure. The inference drawn from these observations is that the aqueous humor is not a simple dialysate.

PYELONEPHRITIS

In previous reviews considerable attention has been given to the renewed interest in chronic pyelonephritis as an insidious disease frequently associated with hypertension and ultimately with failure of renal function. Fahr [13] has recently reviewed the pathologic changes of ascending pyelonephritis, which, he states, is the commonest inflammatory disease of the kidney. Contracted kidneys, which have a struma-like appearance owing to dilatation of tubules and cysts, sometimes show what he regards as evidence of hypogenesis of the renal calices. This developmental defect is regarded by Fahr as a predisposing cause of the ascending infection.

Schaffer and Remsen [14] discuss the relation of urinary infection to chronic nephritis of childhood. Twenty cases in which the diagnosis of chronic interstitial nephritis was made were reviewed. Of these, 15 were undoubted examples of chronic pyelonephritis, yet "pyelitis" had been recognized intra vitam in only 5. Only 1 of the 15 patients was a male. The characteristic features do not lie in the history of the illness; they are to be found in the demonstration of a disproportionate pyuria, of coliform infection of the urine and of anatomic lesions of the genitourinary tract. They believe that the infection is ascending rather than hematogenous. They discuss the possibility that ureteral strictures occur as a result of acute cystitis and that subsequently this results in damage to the upper urinary passages and kidney. Three different types of the malady were observed: (*a*) a type seen in the majority of cases, hypertension and renal insufficiency developing with equal rapidity; (*b*) a type associated with renal rickets but no hypertension as seen in a few chil-

12. Robertson, J. D.: Intraocular Pressure in Nephrotic Oedema and Its Bearing on the Nature of the Aqueous Humor, Lancet **1**:1435 (June 25) 1938.

13. Fahr, T.: Ueber pyelonephritische Schrumpfniere und hypogenetische Nephritis, Virchows Arch. f. path. Anat. **301**:140, 1938.

14. Schaffer, A. J., and Remsen, D.: The Relation of Urinary Infection to Chronic Nephritis in Childhood, Acta pædiat. **22**:415, 1938.

dren, and (*c*) a type characterized by an inordinate degree of hypertension. They conclude that chronic pyuria must be regarded as a serious symptom and that treatment, with the aid of a urologist, must be given early in the course of the disease if disastrous late results are to be avoided. The persistence of pyelonephritis for several months may make fatal renal insufficiency inevitable.

RENAL DISEASE AND PREGNANCY

Peters [15] reviews the evidence of the importance of pyelitis in the "toxemias of pregnancy." Of 203 patients observed, 49 died of renal or vascular disease, 67 had residual renal or vascular disease and 69 had subsequent attacks of "toxemia," leaving only 15 alive without residual incapacity a year or more after the most recent attack of "toxemia." Among the so-called toxemias are to be found conditions resembling all the disorders which outside of pregnancy give rise to arteriolar disease, hypertension or functional impairment of the kidney. Peters can find no evidence of abnormal metabolism or derangement of the endocrine glands in the causation of these disorders. He regards it as probable that the ureteral obstruction of pregnancy predisposes to an unusually severe reaction of the kidney or vascular system to insults which might in the nonpregnant state produce less severe disturbance. It may be that decrease of protein, bicarbonate and sodium and increase of lipoids in the plasma are factors in the heightened susceptibility of the pregnant woman to these disorders. These observations of Peters reveal the fact that "toxemias" of all kinds leave behind them marks which cannot be eradicated. He believes that this warrants the prevention of pregnancy in the woman who has disease of the arteries or kidneys or who has had "toxemia" and the immediate termination of pregnancy on the first sign of hypertension and renal disease.

Regarding the question of the permissibility of further pregnancies after "late toxemia," Wood and Nix [16] state that definite derangement of renal function is the most important contraindication to further pregnancy. If renal function is found to be normal, the advisability of permitting further pregnancy may be determined by repeated observation of the blood pressure and retinas and a consideration of the age factor (older women show a greater tendency to toxemia). These authors recall in this connection that Elden, Sinclair and Rogers found that two thirds of the women with eclampsia whom they studied had low values for urea clearance three months after delivery. Also they

15. Peters, J. P.: The Nature of the Toxemias of Pregnancy, J. A. M. A. **110**:329 (Jan. 29) 1938.

16. Wood, J. E., and Nix, H.: Hypertension in the Late Toxemias of Pregnancy, J. A. M. A. **110**:332 (Jan. 29) 1938.

call attention to the observations by Stander and Peckham, who found that the mortality among pregnant women who had chronic nephritis was 42.5 per cent within ten years, a rate which is five and one-half times the average mortality rate for women in the same age group.

Supporting the ideas expressed by Peters on the nature of so-called toxemias, Page [17] reports that he was unable to demonstrate the presence in the blood of women with eclampsia any pressor substance or toxin or evidence of hypersecretory activity of the pituitary in experiments in which the blood of eclamptic women was transfused into normal pregnant women. As control experiments, normal blood was also given to such women, and observations were made on the blood pressure and urinary output. When the normal donor was given large amounts of solution of posterior pituitary before withdrawal of blood, no antidiuretic response was noted in the recipient.

The retention of water in the last trimester of pregnancy was found by Strauss [18] to amount to as much as 10 per cent of the body weight, whether edema was visible or not. This retention of water is believed to be conditioned by the low protein content of the plasma. If the intake of sodium is kept constant, retention of water is inversely proportional to the osmotic pressure of the plasma protein. Unless the plasma protein is below a certain critical level, a diet consisting of 1,500 cc. of skimmed milk daily will result in the elimination of the retained water. This diet is low in sodium (0.6 Gm.) and relatively high in calcium and potassium. Patients on this diet were tested for periods of five days, and the amount of weight was plotted against the colloid osmotic pressure. Patients whose venous pressure was more than 15 cm. of water were excluded from the tests. Strauss concludes that the retention of water in pregnant women does not differ from that in nonpregnant women.

Various writers propose somewhat different procedures for the management of the toxemias of pregnancy. Dodge and Frost,[19] in view of the low concentration of albumin frequently found in the plasma, recommend giving 80 Gm. of protein daily in the diet. In the discussion of their paper, Thomas Addis pointed out that his observation of pregnant rats showed that it was difficult for the mother rat to ingest sufficient

17. Page, E. W.: The Effect of Eclamptic Blood upon the Urinary Output and Blood Pressure of Human Recipients, J. Clin. Investigation **17**:207 (May) 1938.

18. Strauss, M. B.: Observations on the Etiology of the Toxemias of Pregnancy: IV. The Primary Role of the Plasma Proteins in Conditioning Water Retention and Edema Formation in Normal and Toxemic Pregnancy, Am. J. M. Sc. **195**:723 (June) 1938.

19. Dodge, E. F., and Frost, T. T.: Relation Between Blood Plasma Proteins and Toxemias of Pregnancy, J. A. M. A. **111**:1898 (Nov. 19) 1938.

protein to maintain the plasma protein in normal amount in the presence of the great demand for protein made by the growing fetus. Davis [20] on the other hand, recommends a low protein diet poor in salt and depends on intravenous injections of hypertonic solutions of dextrose to secure diuresis. McPhail [21] recommends ingestion of large quantities of fluid and a diet low in protein.

If convulsions occur Davis [20] recommends the use of morphine, ¼ grain (0.016 Gm.) every hour, until the convulsions cease or the respiratory rate drops to 12. After each convulsion an injection is given intramuscularly of 10 cc. of a 25 per cent solution of magnesium sulfate. Nothing is given to the patient by mouth until after she is conscious, when 50 cc. of 10 per cent Karo syrup is given by stomach tube; this is repeated every hour in amounts increasing by 50 cc. each time until 200 cc. is given.

RENAL HYPERTENSION

The use of the Goldblatt clamp for the production of hypertension through partial ischemia of the kidney is now familiar in many laboratories. A variation of this process has been used by Drury,[22] who puts a loop of silk thread around one renal artery of a young rabbit. As the animals grows, the vessel is gradually constricted, and hypertension results without renal insufficiency, since the other kidney is intact. When the normal kidney is removed the hypertension is increased. Friedman and Katz [23] injected trypsin into both renal arteries and in this way produced chronic renal insufficiency without hypertension. When Goldblatt clamps were applied, the blood pressure rose. If the clamp was applied to one side only, hypertension was noted, but the blood pressure fell again if the ischemic kidney was removed. It is clear, therefore, that renal hypertension is quite independent of renal insufficiency and not dependent on retention of toxic substances.

In 1924 Major and Stephenson tried to associate the guanidine bases with clinical hypertension. Child [24] has reinvestigated this question. He finds that guanidine bases increase in the blood in a manner roughly

20. Davis, M. E.: Water Balance in Relation to the Toxemias of Pregnancy, Surg., Gynec. & Obst. **66**:426 (Feb.) 1938.

21. McPhail, F. L.: Treatment of Toxemias of Pregnancy, J. A. M. A. **111**: 1894 (Nov. 19) 1938.

22. Drury, D. R.: The Production by a New Method of Renal Insufficiency and Hypertension in the Rabbit, J. Exper. Med. **68**:693 (Nov.) 1938.

23. Friedman, M., and Katz, L. N.: Renal Insufficiency Following Trypsin Injection into the Renal Arteries, J. Exper. Med. **68**:485 (Oct.) 1938.

24. Child, C. G.: The Guanidine Bases in the Blood of Dogs with Experimental Hypertension Produced by Constriction of the Renal Arteries, J. Clin. Investigation **17**:301 (May) 1938.

proportional to the increase in nonprotein nitrogen following procedures which produce renal insufficiency. After unilateral ligation of a renal artery the amount of guanidine bases sometimes rose, but only if the nonprotein nitrogen content also rose. No etiologic relation could be established between the experimental hypertension from constriction of the renal arteries and the appearance of guanidine bases in the blood stream. In some animals with hypertension of six to eight months' duration, the values for both blood urea and guanidine bases were within normal limits, though the blood pressure was far above normal.

Comparison of the effects of pressor drugs and the pressor substance found in saline extracts of kidneys has been made by Landis, Montgomery and Sparkman.[25] Saline kidney extracts were heated to 55 to 56 C. and saturated with ammonium sulfate, thus yielding a precipitate which after solution and dialysis produced a conspicuous rise in blood pressure without diminution of the temperature of the skin or of the amplitude of arterial pulsations. Thus the pressor substance produced in the kidney differs from epinephrine, tyramine, guanidine and its derivatives, solution of posterior pituitary, pitressin, ergotoxine and ergotamine, all of which cause a decrease in the temperature of the skin and a diminution in the blood flow in the ear of the heated rabbit.

A study of the renal arteries in relation to age and arterial hypertension has been made by R. H. Williams and T. R. Harrison.[26] Three groups of patients were investigated post mortem: (*a*) elderly persons with benign hypertension, in whom the predominant change was narrowing of the large renal arteries; (*b*) middle-aged persons with malignant hypertension, in whom the predominant change was narrowing of the afferent arterioles to the glomeruli, and (*c*) young hypertensive patients with glomerulonephritis, who showed narrowing of the renal arterioles. Rosenberg, Keith and Wagener[27] found lesions of the renal arteries associated with mild or fluctuating hypertension, while in patients with sustained hypertension they found lesions of the arterioles. Leiter[28] reports a case of hypertension coming on acutely in a man who had extensive bilateral thromboarteritis of the small renal arteries.

25. Landis, E. M.; Montgomery, H., and Sparkman, D.: The Effects of Pressor Drugs and of Saline Kidney Extracts in Blood Pressure and Skin Temperature, J. Clin. Investigation **17**:189 (March) 1938.

26. Williams, R. H., and Harrison, T. R.: A Study of the Renal Arteries in Relation to Age and to Hypertension, Am. Heart J. **14**:645 (Dec.) 1937.

27. Rosenberg, E. F.; Keith, N. M., and Wagener, H. P.: Diffuse Arterial Disease with Hypertension: Two Unusual Cases of Contrasting Types, Arch. Int. Med. **62**:461 (Sept.) 1938.

28. Leiter, L.: Unusual Hypertensive Disease, J. A. M. A. **111**:507 (Aug. 6) 1938.

Freeman and Hartley [29] record the case of a patient who had unilateral nephrectomy for traumatic rupture of the kidney. Subsequently hypertension developed, and at autopsy the orifice of the large artery of the remaining kidney was greatly narrowed by an atheromatous plaque. The foregoing observations show the conditions of the arteries which are associated with partial ischemia of the kidneys and hypertension.

Rytand [30] demonstrated that the elevation of blood pressure which is observed in persons with coarctation of the aorta is due to the action of the pressor substance formed in the ischemic kidneys. In experiments on animals, if the aorta was constricted proximal to both renal arteries, hypertension resulted if there was living renal tissue. No elevation of blood pressure occurred if nephrectomy had been done, although the mechanical effects of aortic constriction were the same.

Grossman and Williams [31] gave extracts containing renal pressor substance to rats of various ages. The doses administered were proportional to the body surfaces of the animals. The youngest rats showed the least and the oldest the greatest pressor response. When the kidneys of young and old rats were assayed for pressor substance, the greater amounts were found in those of young rats and the lesser in those of old rats. They comment on these experiments in relation to the fact that a larger proportion of elderly than of young persons exhibit hypertension.

High blood pressure is sometimes found in association with hydronephrosis. This phenomenon was investigated by Williams, Wegria and Harrison,[32] who observed well marked hypertension in rats with spontaneous bilateral hydronephrosis. Such rats gave a greater pressor response when they received injections of renal pressor substance. Furthermore, extracts prepared from hydronephrotic kidneys gave greater pressor effects than those derived from normal kidneys. The same results were obtained when the hydronephrosis was produced by ligation of the ureters.

STUDIES OF RENAL FUNCTION

Chesley [33] has studied urea clearance during oliguria. When the volume of urine falls below 0.35 cc. per minute, the urea concentration

29. Freeman, G., and Hartley, G.: Hypertension in a Patient with a Solitary Ischemic Kidney, J. A. M. A. **111**:1159 (Sept. 24) 1938.

30. Rytand, D. A.: The Renal Factor in Arterial Hypertension with Coarctation of the Aorta, J. Clin. Investigation **17**:391 (July) 1938.

31. Grossman, E. B., and Williams, J. R., Jr.: Relation of Age to Renal Pressor Substance, Arch. Int. Med. **62**:799 (Nov.) 1938.

32. Williams, J. R., Jr.; Wegria, R., and Harrison, T. R.: Relation of Renal Pressor Substance to Hypertension of Hydronephrotic Rats, Arch. Int. Med. **62**: 805 (Nov.) 1938.

33. Chesley, L. C.: Urea Excretion at Low Urine Volumes: The Calculation of "Minimal" Urea Clearances, J. Clin. Investigation **17**:119 (March) 1938.

ratio becomes fixed so that further decrease in volume does not affect the ratio of urine urea to blood urea. A formula is suggested by means of which these minimal clearances can be related to those obtained under standard or maximal conditions. In a subsequent paper Chesley [34] reports that with low urinary volumes, urea and creatinine become maximally concentrated in the urine. The plasma clearance values for endogenous creatinine have a linear arrangement in the range of urinary volumes of 0.35 to 0.5 cc. per minute; this suggests that these urinary volumes vary directly with the rate of glomerular filtration and implies a constant and maximal resorption of water.

Attempts are now being made to study separately and quantitatively tubular and glomerular function. Smith, Goldring and Chasis [35] find that phenolsulfonphthalein, diodrast and hippuran are excreted by a common cellular mechanism in the tubules. This tubular action has a maximal limiting value; hence these authors take maximal clearances of these three substances as a measure of the tubular mass. Glomerular filtration is measured by the inulin clearance. From data on these observations the authors calculate the renal blood flow at about 1,300 cc. per minute and the glomerular filtration at 137 cc. per minute for a man with a surface area of 1.73 square meters under basal conditions.

Chasis and Smith [36] studied the simultaneous excretion of urea and inulin. In the case of inulin the ratio of values for the urine and the plasma is a measure of the degree of concentration of the glomerular filtrate. The urea clearance was less than the volume of the filtrate in both normal and nephritic subjects, showing that urea is invariably resorbed to some extent. It was found that as the capacity of the tubule to resorb water is impaired by disease, the fraction of urea resorbed decreases, so that the value of the urea clearance approaches that for glomerular filtration. There was no evidence in any case to indicate an increased back diffusion of urea.

A somewhat contrary view is presented by Nicholson, Urquhart and Selby.[37] These investigators produced injury to one kidney by perfusing it with sodium tartrate, leaving the other intact. The nephrosis produced was limited to the proximal convoluted tubule, with no histologic evi-

34. Chesley, L. C.: Renal Excretion at Low Urine Volumes and the Mechanism of Oliguria, J. Clin. Investigation **17**:591 (Sept.) 1938.

35. Smith, H. W.; Goldring, W., and Chasis, H.: The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, J. Clin. Investigation **17**:263 (May) 1938.

36. Chasis, H., and Smith, H. W.: The Excretion of Urea in Normal Man and in Subjects with Glomerulonephritis, J. Clin. Investigation **17**:347 (May) 1938.

37. Nicholson, T. F.; Urquhart, R. W. I., and Selby, D. L.: Renal Function as Affected by Experimental Unilateral Kidney Lesions: Nephrosis Due to Sodium Tartrate, J. Exper. Med. **68**:439 (Sept.) 1938.

dence of glomerular damage. After perfusion of the kidney the bladder was opened, and separate functional studies were made of each kidney. The excretion of water and of chloride was disturbed in the injured kidney, and the clearances of urea, xylose, inulin, creatinine and phenolsulfonphthalein were diminished. The clearance of ferrocyanide was diminished; this substance was found in the damaged tubular cells of the injured kidney but not in the normal one. Hence the authors hold that increased back diffusion may render inulin and creatinine unsuitable for the measurement of glomerular filtration in conditions in which the tubules are damaged.

Chasis, Ranges, Goldring and Smith [38] made observations on water diuresis and the action of oil of juniper, epinephrine, theophylline, caffeine, sodium nitrate and artificial fever, in which the total renal blood flow and the glomerular filtration were estimated. Their experiments led to the conclusion that the blood flow of the kidney is regulated by the efferent renal artery. Since an increase or decrease in blood flow is accompanied by inverse changes in the filtration fraction, the rate of filtration tends to be independent of the normal variations in renal blood flow. It is believed that the vasomotor control of the efferent artery is independent of the mechanism by means of which the blood pressure is regulated through the carotid sinus.

RENAL INSUFFICIENCY FOLLOWING BLOOD TRANSFUSION

DeGowin, Warner and Randall [39] have thrown new light on the mechanism of renal insufficiency occurring in incompatible blood transfusions. Transfusion of canine hemoglobin into dogs when the urine is acid results in death from renal insufficiency. This does not occur when the urine is alkaline. The anatomic picture was that of obstruction of the tubules by pigment when the urine was acid. In 9 patients who died of renal insufficiency following hemolysis, two processes were observed: (1) the obstruction of tubules with pigment and (2) a degeneration of tubular epithelium and interstitial edema. The obstruction of tubules might be prevented if the urine was alkalinized prior to the transfusion, but the authors doubt whether the nephrotoxic process would be limited by that procedure.

38. Chasis, H.; Ranges, H. A.; Goldring, W., and Smith, H. W.: The Control of Renal Blood Flow and Glomerular Filtration in Normal Man, J. Clin. Investigation **17**:683 (Sept.) 1938.

39. DeGowin, E. L.; Warner, E. D., and Randall, W. L.: Renal Insufficiency from Blood Transfusions: II. Anatomic Changes in Man Compared with Those in Dogs with Experimental Hemoglobinuria, Arch. Int. Med. **61**:609 (April) 1938.

Correspondence

ELECTIVE LOCALIZATION AND INFECTIONS OF THE RESPIRATORY TRACT

To the Editors:—Polemics should have no place in science. I have consistently refrained from them and shall continue to refuse to try to convince by argument alone those whose views are at variance with my own. Differences founded on experiment I have considered from time to time as occasion demanded by the presentation of new or additional data and, incidental to these, have indicated so far as possible wherein lay the reason for the discrepancies.

The statements by Reimann with regard to my work on elective localization and on the use of vaccines in cases of infections of the respiratory tract are so misleading as to require consideration.[1] I can point out only (1) that from his list of diseases in which I have presented evidence indicating streptococci as the etiologic factors, he omitted four—ulcer of the stomach and duodenum, cholecystitis and gallstones, canine encephalomyelitis and equine encephalomyelitis—and that he neglected to state that my results have been corroborated by my associates and independently by others for most of the diseases he listed; (2) the he neglected to mention the fact that Schottmüller was the only person who really voiced disagreement with my views on elective localization at the German Congress of Internal Medicine at Wiesbaden; (3) that Schottmüller admitted in the open discussion on that occasion that the principle of elective localization was applicable in some cases; (4) that the discussion or rather presentation of confirmatory studies by many, some of whom voiced emphatic disagreement with Schottmüller's views, exceeded fourfold the allotted time for my paper, and (5) that in making rounds with Schottmüller several weeks later, an invitation I accepted at the time of the congress, I found much evidence of focal infection in his patients which had been entirely overlooked by him. Infection was actually demonstrated in 5 patients during my short visit. One had recurring attacks of cholecystitis, 2 had suffered from rheumatic fever for about two months and 2 had acute iritis. A history of an attack of acute tonsillitis shortly before the onset of the systemic disease was elicited in each of these cases, and large amounts of liquid pus were expressed from the tonsils of each by the method my colleagues and I use. Acute pulpitis with death of the pulp and draining dental sinuses occurred shortly before the attack in each of the 2 cases of acute iritis. And, finally, Schottmüller himself had been at home in bed ill with an unexplained fever for some time prior to my visit. It was clearly evident that he was an example of the very problem under discussion. His teeth were literally floating in pockets of pyorrhea, and his breath was terrible. He died several years later of cardiac failure.

In regard to Reimann's criticism of the work which Heilman and I [2] have done on the prevention and treatment of colds and influenza, I am impelled to record the following statements: It is generally conceded, as indicated in our paper, that the initial symptoms in colds and influenza are associated with the virus and that

1. Reimann, H. A.: Infectious Diseases: Review of Current Literature, Arch. Int. Med. **62**:305-352 (Aug.) 1938.

2. Rosenow, E. C., and Heilman, F. R.: Streptococcal Vaccines in the Prevention and Treatment of Respiratory Infections, Am. J. Clin. Path. **8**:17-27 (Jan.) 1938.

organisms of the pneumococcus-streptococcus group are the chief cause of the subsequent symptoms, lesions, complications and death. The strains of these organisms from persons having colds or influenza possess on isolation characteristic pneumotropic virulence and other specific properties which they promptly lose on cultivation on artificial mediums. They become like the strains isolated from the throats of well persons remote from an epidemic of infections of the respiratory tract.[3] In previous work[4] the value of vaccines prepared from freshly isolated strains of this group of organisms was demonstrated in animals and on a large scale in human beings during the pandemic of influenza of 1918 to 1920. The vaccinated patients as compared with the unvaccinated controls fared from three to twelve times better as regards the rate of attack, incidence of pneumonia, hemorrhagic edema of the lungs, empyema and encephalitis. It seems (1) that Reimann overlooked the fact that our results obtained in human beings, especially in prevention, were so overwhelmingly favorable whenever the vaccine was used as to leave no doubt of its value; (2) that the vaccine actually used for human beings protected animals against infection by streptococci regularly at hand in these diseases; (3) that he failed to consider the fact that our vaccine was prepared from strains freshly isolated in dextrose brain broth after preservation in dense suspension of glycerin (two parts) and 25 per cent salt solution (one part); that vaccines prepared in this way are much less toxic and more immediately antigenic and hence more suitable for treatment than vaccines prepared directly in the usual manner from streptococci, often after almost indefinite cultivation on artificial mediums, and (4) that he seems to have missed completely the remarkable fact that a vaccine prepared in 1937 from four hundred strains of streptococci isolated during the pandemic of 1918 to 1920 and preserved in the glycerin-salt solution menstruum protected animals against the streptococcus isolated from persons ill with influenza during an epidemic in 1937. This vaccine was not used for human beings, as stated by him, but instead vaccines prepared from a number of more recently isolated strains.

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3. Rosenow, E. C.: Cataphoresis as a Control of Specificity of Streptococcal Vaccines: Influenzal Streptococcus Vaccine in the Prevention and Treatment of Infections of the Respiratory Tract, J. Immunol. **26**:401-433 (May) 1934.

4. Rosenow, E. C.: Studies in Influenza and Pneumonia: IV. Further Results of Prophylactic Inoculations, J. A. M. A. **73**:396-401 (Aug. 9) 1919.

News and Comment

NEWS AND COMMENT

American Board of Internal Medicine, Inc.—Written examinations for certification by the American Board of Internal Medicine will be held in various sections of the United States on the third Monday in October 1939 and the third Monday in February 1940.

Formal application must be received by the secretary before Aug. 20, 1939 for the examination on Oct. 16, 1939, and on or before Jan. 1, 1940 for the examination on Feb. 19, 1940.

Application forms may be obtained from Dr. William S. Middleton, secretary-treasurer, 1301 University Ave., Madison, Wis.

Book Reviews

Investigations on Epilepsy and Water Metabolism. By H. P. Stubbe Teglbjaerg. Pp. 247. Copenhagen: Levin & Munksgaard, 1936.

In this monograph Teglbjaerg reports the results of studies on the metabolism of water in cases of epilepsy and the effects of variations in the intake of water on the frequency of seizures. The work was done in the Filadelfia colony for epileptic patients in Dianalund, Denmark. The author assumes that there is a dualistic pathogenesis of epilepsy—a "cerebral factor," in the form of a disease of the brain, and a "humoral factor" of constitutional origin, resulting in a lowered threshold for convulsions. In cryptogenic epilepsy the cerebral factor is not demonstrable, but its presence must be assumed, chiefly by analogy. The arguments for the humoral factor include the precipitation of seizures by hyperventilation in a high percentage of cases, the failure of trauma and tumors to produce epilepsy in many cases and the tenfold greater frequency of epilepsy among relatives of epileptic patients than among "normal" persons. To these arguments Teglbjaerg adds the beneficial effects of a ketogenic diet, inanition and dehydration.

The studies on which the monograph is based include an investigation of the water balance of normal and of epileptic subjects. Attention was paid not only to the free water administered to the patients but also to the constitutional and oxidation water of the food, which represents about one-half the amount available to the subjects. The balance of sodium chloride was also studied, as well as the effects of various diuretics and the antidiuretic pitressin. The "spontaneous water balance" was found to be more unstable in epileptic than in normal persons, but no relation was discovered between the seizures and the spontaneous retention of water or changes in the volume of blood. The frequency of seizures was lowered but not abolished by dehydration and was increased by hydration. Extensive and careful studies of insensible perspiration failed to yield any significant information as to the water regulation of the organism, either in normal or in epileptic persons. The pressure of the cerebrospinal fluid was likewise found to be normal between seizures in epileptic patients and to be practically unaffected by the injection of physiologic or hypertonic solutions of sodium chloride or dextrose. Others have shown, however, that hyperhydration plus the antidiuretic effect of pitressin does increase the cerebrospinal fluid pressure.

Teglbjaerg concludes from his studies that though the frequency of seizures in epileptic patients is increased by hydration and decreased by dehydration, there does not appear to be any gross change in the water balance or in the cerebrospinal fluid pressure which might explain the seizures. He thus discards completely the mechanical pressure theory of Temple Fay as being unsupported by the facts. He adheres rather to the view of McQuarrie that an important part of the constitutional factor in epilepsy is a disturbance in the cellular susceptibility to hyperhydration. He thinks that this susceptibility may be an altered permeability of the cell membrane, especially since disturbances have been found in the lecithin-cholesterol quotient of the blood of epileptic patients and since these lipoids have a great influence on the permeability of the cell membrane. He states, however, "It will be a question of words rather than of realities whether one wishes to ascribe the epileptic seizures to a sudden change in the surface tension of the cell, or in the ion milieu of the cell."

This work of Teglbjaerg, amply documented with charts and graphs, represents an important contribution to an understanding of the intimate nature of epilepsy. His facts, which seem securely established, are nevertheless not yet easy to incorporate in a consistent theory of epilepsy. An excess of water is not the only factor

that will precipitate seizures in epileptic patients, nor will it serve to bring them on in all such patients. While many epileptic patients are sensitive to hydration, that is not equivalent to saying that spontaneous seizures are due to a disturbance in the metabolism of water. In fact, Teglbjaerg's work in some respects seems to render this unlikely. On the other hand, a valuable therapeutic weapon is at hand in dehydration, properly carried out. Although an ultimate understanding of epilepsy appears almost as distant as ever, any thoroughgoing explanation must account for the role played by water in the causation of seizures. To such an explanation this monograph is an important preliminary.

Oreille interne: Etude anatomo-pathologique et clinique; technique histologique et expérimentale. By C. Claoué. Second edition. Paris: Norbert Maloine, 1938.

Convinced that anatomy and biology constitute the foundation on which medical education—especially the training of the specialist—should be based, Dr. Claoué has written an instructive textbook on the internal ear. There is a short introductory chapter on development which leads to an account of maldevelopments met with in practice, as well as of the neurovascular pathways along which infection may spread from the ear to the subarachnoid spaces.

The main text is divided into three parts: The first deals with anatomic, pathologic and clinical considerations of the inner ear; the second, with the technic of microscopic examination, and the third, with a study of the ear of the guinea pig. In the first part the inner ear is described, region by region, in separate chapters, each being introduced by a short anatomic review. Thus the first chapter deals with the osseous capsule—its formation and its more common lesions—otosclerosis, rickets and Paget's disease. Then follows a chapter descriptive of the perilymph spaces, with a consideration of their invasion by infections, especially those associated with removal of granulations in the middle ear and of curettage of its medial wall. The chapter on the endolymph spaces contains a description of the degeneration in the membranous labyrinth which may accompany general diseases, such as leukemia and syphilis, as well as the pathologic picture of occupational deafness. This is followed by a chapter on the internal auditory meatus. The fifth chapter may be said to be a general summation of the four previous chapters. As an addendum the author has a chapter on the technic of opening the internal auditory canal from the middle ear and the operative treatment of labyrinthine meningitis.

This method of considering lesions of the inner ear makes the book of great value not only to the otologists but to the general practitioner who desires an understanding of the lesions met with in the course of his practice. The author is to be congratulated not only on this presentation but also on the numerous and apt illustrations which add to the clarity of the text.

Hypervitaminosis D, belyst gennem kvantitative overdoseringsforsøg. By Axel Guldager. Pp. 219, with 14 illustrations. Copenhagen: Nyt Nordisk Forlag, Arnold Busck, 1936.

This dissertation is concerned with the question of whether the poisoning produced by excessive doses of preparations of vitamin D is true hypervitaminosis or merely poisoning due to substances difficult to separate from the vitamin. The author is convinced that he dealt with true hypervitaminosis D in his experiments because preparations from three independent sources, when used on mice and rats, gave the following results: No qualitative difference was found in the symptoms produced by the three commercial preparations as compared with those produced by purified vitamin D. Quantitative comparison showed the toxicity to be proportional to the vitamin content, within the limits of experimental error. Doses which were harmless when given daily over short periods sometimes caused

typical symptoms of hypervitaminosis if continued for longer periods, but sufficiently small doses, of 1,400 to 1,500 U. S. P. units per day, were continued for half a year without cumulative effects. Lack of vitamin A in the diet increased the sensitiveness of the animal to excess of vitamin D. Lack of vitamin B similarly increased the sensitiveness of rats to excess of vitamin D. Increasing the intake of vitamin B above its optimum did not protect against excess of vitamin D. Increasing the calcium in the diet increased the sensitiveness of mice to vitamin D so markedly that an otherwise harmless dosage of vitamin D was made markedly toxic thereby. The effect of phosphates was similar to that of calcium, though less marked. Gravid mice were unaffected by doses that had been found toxic for nongravid mice.

The Vitamins and Their Clinical Application. By Dr. Wilhelm Stepp, Dr. Joachim Kühnau and Dr. Hermann Schroeder. Translated by Herman A. H. Bouman. Price, $4.50. Pp. 173. Milwaukee: The Vitamin Products Co., 1938.

The purpose of this small book is to give to the average physician a bird's-eye view of the rapidly developing field of vitamins. To write a concise review of a new and expanding field of science is an extremely difficult and nearly impossible task, since apparent and well established facts may become obsolete in a short time. The authors have done well in presenting this complicated subject in such a compact and simple manner. In many instances, seemingly dogmatic statements are made, obviously to carry the reader over a vast and contested experimental field. In discussing the therapeutic application of vitamin therapy the writers mention many instances in which reported benefits are based on only 1 or more case reports, and such statements may be misleading if one is not acquainted with the literature on the particular subject.

In all, this book should be very useful for one who wishes to obtain a rather quick and concentrated dose of "vitamin knowledge." The bibliography is adequate (one third of the book) but not complete, and a large number of the references are naturally to German articles. It is to be remembered that since this book went to press there has been considerable advance in knowledge of vitamins; such substances as nicotinic acid and vitamin K are conspicuous by their absence.

Undersøgelser over calciumudskillelse. By Harald Christiansen. Pp. 108. Copenhagen: Nyt Nordisk Forlag, Arnold Busck, 1936.

This excellent thesis contradicts, on the basis of painstaking work, the long-accepted idea that the intestinal tract is the excretory organ for calcium. After a review of the conflicting reports on the subject, the author presents his own experiments on rabbits and goats. Feces, urine, bile, milk and various organs were analyzed for calcium, and the calcium balance was studied during inanition, during periods in which diets low in calcium were given and during periods of slow, continuous intravenous injections of solution of calcium salts.

The results disclosed the existence of a slow, irregular loss of calcium by way of the gastrointestinal tract. The intravenous administration of calcium did not accelerate this loss and did not increase the amount of calcium in the bile. Neither did it accelerate the secretion of calcium in the milk. It did, however, increase the urinary output and the amount stored in the kidneys. The kidneys were the only organs except the bones that showed an increased calcium content after the injections. Other evidence corroborated the view that the kidneys govern calcium balance by regulating their output of the element. Fatalities during slow injections were found to be caused not by hypercalcemia directly but by excessive retention of the element in the substance of the kidneys, with consequent nephritis and uremia. This helps to explain the nephritis of hyperparathyroidism and hypervitaminosis D.

A Monograph on Veins. By Kenneth J. Franklin, D.M., M.R.C.P., Tutor and Lecturer in Physiology, Oriel College; University Demonstrator of Pharmacology, Assistant Director of the Nuffield Institute for Medical Research, Oxford. Price, $6. Pp. 410, with 46 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

This book is a rather attractive and readable exposition on veins from the standpoint of physiology. It contains a comprehensive and detailed review of the historical development of the knowledge of veins and their physiology. According to the author's statement, this book is primarily intended for those engaging in researches on the vascular system and the circulation of the blood. From the standpoint of the general student of the subject the amount of space devoted to the review of the literature on venous physiology seems a little too extensive, and an adequate summary is lacking. The chapter at the end of the book on clinical aspects is disproportionately brief, dismissing many interesting and controversial points too quickly. There is little in the book concerning the pathology and pathogenesis of lesions of the veins. Thus, to the reader who is interested solely in the diseases of the veins and their treatment the book may be somewhat disappointing. To the student who is interested in some problem in the physiology of the circulation it should be a valuable summary and reference guide.

Undersøgelser over testis histopathologi ved E-avitaminose: En eksperimentel-morphologisk studie. By Axel Ringsted. Pp. 191, with 30 illustrations. Copenhagen: Nyt Nordisk Forlag, Arnold Busck, 1936.

This dissertation contains a review of the subject of vitamin E and a presentation of the author's own experiments on the rat. The sterility caused by lack of vitamin E affects not only the female but the male. In the latter the gradual testicular degeneration was followed in great detail up to four hundred and sixty days after institution of the deficient diet. The earliest changes were in the seminiferous elements, but later the interstitial tissue also suffered extreme atrophy. The degeneration was never uniform throughout a testicle; even in a maximally deteriorated organ a few well preserved seminal tubules persisted. While some of these changes were nonspecific, others seemed to be diagnostic of lack of vitamin E and therefore possibly of use in the development of methods of assay. For any one who may undertake research on the antisterility vitamin, this book, with its excellent photomicrographs and its wealth of detail as to dietary and histologic technic, will be a prerequisite.

The Compleat Pediatrician. By Wilburt C. Davison. Second edition. Price, $3.75. Pp. 274. Durham, N. C.: Duke University Press, 1938.

The "index of symptoms method" of writing a textbook has been somewhat discredited in the past, but Dr. Davison has overcome its defects and produced a really valuable compendium. The explanation of success in this case is not far to seek: The writer knows what he is talking about, the literature is thoroughly covered and the style has clearness, force and precision. As a vade mecum and an aid to quick orientation as to diagnosis and procedure, it should be (as the need for a second edition shows) invaluable not only to the pediatrician but to the general physician.

Le traitement de la tuberculose pulmonaire par la tuberculine. By Dr. M. Jaquerod. Price, 2.50 francs. Pp. 43, with 2 illustrations. Lausanne: Librairie Payot & Cie, 1937.

This small pamphlet deals with tuberculin therapy as practiced by the author at present. It presents little or nothing that is new, and to the American reader it appears a bit optimistic. In spite of the case which is made out by the author, it is doubtful if this pamphlet will obtain many converts to tuberculin therapy in this country.